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The Archives of Internal Medicine

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

L. STUDIES ON THE CONTROL OF HUNGER BY DRUGS *

HARRY GINSBURG, S.B.† AND ISIDOR TUMPOWSKY, S.M., M.D.

CHICAGO

The hunger mechanism is a local mechanism within the stomach itself, subject to central regulation. A great accumulation of well established data points to the fact that hunger is a sensation produced by an increase in intragastric tension.[1] This is produced by characteristic contractions of the empty or nearly empty stomach beginning in the fundic region. Physical attitudes and local pathologic conditions, as ulcer or pyloric constriction, interpret tension as pain.[2]

Stomach activity is influenced by peripheral nervous control.[3] The vagus nerve carries impulses stimulating tone and peristalsis; the splanchnics contain inhibitory fibers. By these two paths central action is exerted. It has been found, however, that with both vagi and splanchnics sectioned the stomach regains the tone temporarily lost, and the typical muscular activity of the stomach is resumed. This suggests a mechanism inherent in the stomach itself which regulates motor activity. The anatomic basis of such a system may be found in a nodal system which Keith[4] has recently described in the stomach wall comparable to the nodal system of the heart.

Manipulation of the hunger contractions has been carried out by changing mental states and the administration of various substances. Excitement, fear and anger inhibit hunger.[5] This comes well within the experience of the individual. Tracings from the stomach demonstrate that the hunger contractions in these conditions are inhibited. Water, acids, alkalis, and food taken by mouth or placed directly into

* Submitted for publication July 10, 1918.

* From the Hull Physiology Laboratory of the University of Chicago.

† Mr. Ginsburg died during the course of the work for which he furnished the inspiration.

1. Carlson: Am. Jour. Physiol., 1913, **31,** 175.
2. Hertz: Sensibility of the Alimentary Canal, London, 1913, p. 47. Ginsburg, Tumpowsky and Hamburger: Jour. Am. Med. Assn., 1916, **67,** 990. Hardt: Jour. Am. Med. Assn., 1918, **70,** 837.
3. Carlson: Am. Jour. Physiol., 1913, **32,** 369.
4. Keith: Lancet, London, 1915, **2,** 371.
5. Carlson: Am. Jour. Physiol., 1913, **32,** 376.

the stomach by tube or through a fistula also inhibit contractions.[6] Fever associated with anorexia inhibits contractions,[7] while in the cachexia of advanced pulmonary tuberculosis with chronically high temperature they may be extremely vigorous.[8] In starvation[9] and experimental pancreatic diabetes[10] contractions are marked. The effects of drugs on stomach activity has not been emphasized nearly to the degree that the intestine has been studied from this standpoint. Some facts in this regard have already been established clinically. The present work was undertaken to determine the effects of various common drugs on the hunger contractions by the use of the balloon method.

EXPERIMENTAL METHODS

Gastric fistulae were produced in twelve dogs, and in four of these both vagi and splanchnics were cut. In the latter cases it has been found advisable to section the splanchnics first, inasmuch as this part of the preparation is the most difficult and attended with the greatest fatality. The major splanchnic is severed as it emerges from the diaphragm. On the left side it lies lateral to the adrenal, running toward the gland parallel with the large adrenal vein. The right splanchnic is more difficult to obtain because the liver hampers good exposure and the nerve very frequently lies beneath the vena cava. Hemorrhage from the many small retroperitoneal veins about the adrenal makes the operation more difficult because other structures are easily mistaken for the nerve. Occasionally pneumothorax is produced by exploring the edge of the diaphragm, but this is not fatal. In about two weeks the vagi may be severed. Incision is made in the eighth or ninth interspace on the left side and somewhat posteriorly. The esophagus is hooked up through the interspace; the right and left vagus lying posteriorly and anteriorly, respectively, are grasped in a hemostat and a piece excised. All branches are similarly treated, and the wound is quickly closed. If the operation is done hurriedly, that is to say, two or three minutes elapsing from opening to closure of the pleural cavity, artificial respiration is not necessary. In fact, we used artificial respiration but twice, and lost but one animal at this stage, an accident which, with the technic developed subsequently, might have been avoided. If the animal shows signs of difficulty the edges of the wound may be approximated with the fingers until respirations become more regular, and the operation may then pro-

6. Carlson: Am. Jour. Physiol., 1912, **31,** 151, and 1913, **32,** 389.
7. Meyer and Carlson: Am. Jour. Physiol., 1917, **44,** 222.
8. Meyer, Jacob: Contribution, Hunger in Tuberculosis, to be published.
9. Carlson: Am. Jour. Physiol., 1914, **33,** 95.
10. Luckhardt: Am. Jour. Physiol., 1914, **33,** 313. Luckhardt and Hamburger: Jour. Am. Med. Assn., **66,** 1831.

ceed. In one case the heart stopped pulsating for about one minute. By rapid and vigorous massage of the heart directly with two fingers through the intercostal space to imitate as nearly as possible the force and rate of the heart, pulsations recovered slowly and very feebly at first, finally at the usual rate and strength as near as one could determine. The dog recovered and lived many weeks, dying from respiratory infection. This result could not be repeated in other conditions and was probably due to recovery from reflex stimulation of the vagus. The gastric fistula was made through the left rectus to make use of the valve action of that muscle. A cone of stomach was drawn through the opening and the serosa stitched to the peritoneum, fascia and skin by three or four stitches in each layer. The apex was opened and the mucosa tacked to the serosa by three loose stitches.

The drugs were used on both sets of animals, those with the "intact" stomach having the nerves intact, and those with the "isolated" stomach having the peripheral nerves sectioned. The animals were easily trained to lie on the laboratory tables in a moderately darkened room with a towel covering the head to keep out the light and prevent their disturbance from such outside factors as the presence of others in the laboratory and the manipulations of the observer. It was possible in this way to have four animals running together while a single observer manipulated the kymographs, administered the drugs and recorded observations. One finds that the dogs will lie on the plain, uncovered table, not requiring soft blankets. They become so accustomed to the routine that they choose the proper laboratory by preference when released from the kennels, and lie quietly until the balloon is removed from the stomach at the end of the observation, when they sense their liberty and jump from the table. The animals are so astonishingly quiet during observations that other workers coming into the room unfamiliar with the work think the dogs are anesthetized. Subcutaneous and even intravenous injections may be made without disturbing the animal. One can, unassisted, apply the constrictor to the leg, plunge the needle into the vein, remove the constrictor and inject without causing the animal to change his position. Hypodermic and intramuscular injections require no assistance.

RESULTS

Atropin.—Auer and Meltzer[11] assert that atropin causes paralysis of the vagus endings connected with the ganglia of Auerbach's plexus and that the action is on the myoneural junction. Cushny[12] believes that the terminations are not paralyzed, because small doses only arrest

11. Auer and Meltzer: Am. Jour. Physiol., 1906, **17**, 17.
12. Cushny: Pharmacology and Therapeutics, Philadelphia and London, 1913.

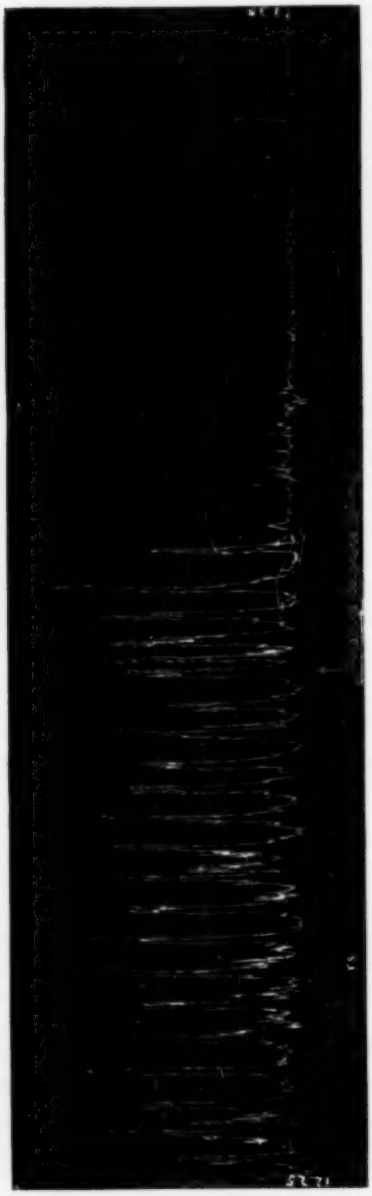

Fig 1.—Atropin, 1/80 grain subcutaneously, causing complete inhibition in seven minutes lasting hours.

certain abnormal violent forms of contractions without interfering with normal peristalsis. He also says that larger doses increase, and very large doses paralyze, the latter probably never occurring in the intact animal. Clinically, belladonna relieves some spasmodic conditions of the stomach by paralyzing the vagus and allowing unopposed action of the splanchnics.[13] Fluoroscopic examination has shown that

TABLE 1.—ATROPIN

Stomach	Administration	Dose, Grain	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1/80	Inhibition	7		
Intact	Subcutaneous	1/80	Inhibition	10		
Intact	Subcutaneous	1/80	Inhibition	14	.....	Eserin, 1/80 grain given 23 minutes after inhibition began yielded contractions in 23 minutes
Intact	Subcutaneous	1/70	Inhibition	8	3 hrs. 40 min. then contractions	Occasional contractions "escaped"
Intact	Subcutaneous	1/70	Inhibition	5		
Intact	Subcutaneous	1/60	Inhibition	7	1 hr. 40 min.+	
Intact	Subcutaneous	1/60	Inhibition	5	1 hr.+	36 minutes after pilocarpin 1/6 grain
Intact	Subcutaneous	1/60	Inhibition	5	.....	1 hour 30 minutes after eserin 1/60 grain
Intact	Subcutaneous	1/50	Inhibition	4	30 min.+	
Intact	Subcutaneous	1/100	Inhibition	8	.....	50 minutes after pilocarpin 1/12 grain
"Isolated"	Subcutaneous	1/50	Inhibition	8	1 hr.+	17 minutes after pilocarpin 1/6 grain
"Isolated"	Subcutaneous	1/40	Inhibition	8	4 hrs.+	Pituitary extract (Armour) ampule intravenously; 3 hours after followed by small infrequent contractions
"Isolated"	Subcutaneous	1/40	Inhibition	10	1 hr. 20 min.+	1 hour 52 minutes after pilocarpin 1/6 grain

often the spasm is suddenly relieved, while in other cases shown to be spasmodic by the massage test, it has no effect. Hertz[14] says that belladonna is remarkably efficient in hour glass contractions of spasmodic origin and may even relieve spasm in the presence of active ulceration. In our work atropin sulphate in doses from $\frac{1}{80}$ to $\frac{1}{40}$ grain hypodermically invariably inhibited contractions and counteracted the

13. Barclay: Alimentary Tract: A Radiographic Study, New York, 1915, p. 17.

14. Hertz: See reference Footnote 2, p. 76.

effect of pilocarpin and eserin in this regard. The time of action is quite constantly between five and ten minutes. The inhibition is sudden, decisive and persists for hours. Occasionally a few undulations "escape." Otherwise the tracing records only the respiratory oscillations. The fact that the same results obtain in "isolated" stomach indicates that the action is on the myoneural junction.

TABLE 2.—PILOCARPIN

Stomach	Administration	Dose, Grain	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1/5	Increased tonus	8	20 min.	25 minutes after epinephrin (adrenalin), 2 c.c. 1:10,000 intravenously and subcutaneously
Intact	Subcutaneous	1/5	Contractions	5	45 min.+	
Intact	Subcutaneous	1/75	No effect			
Intact	Subcutaneous	1/75	Slight increase	.....	2 hrs.+	Gradual increase after second dose
Intact	Subcutaneous	1/6	Contractions	8	1 hr. 30 min.+	Gradual increase in tonus preceded the contractions, later inhibited by atropin
Intact	Subcutaneous	1/12	Contractions	15	50 min.	Inhibited by subsequent atropin
Intact	Subcutaneous	1/12	Contractions	9	.....	40 minutes after pituitary extract
"Isolated"	Subcutaneous	1/6	Contractions	8	1 hr. 30 min.+	Increase in tonus preceded contractions; inhibited by subsequent atropin
"Isolated"	Subcutaneous	1/5	Contractions	6	1 hr.	46 minutes after eserin 1/40 grain
"Isolated"	Subcutaneous	1/6	Contractions	3	.....	Inhibited by atropin 20 minutes later

Pilocarpin.—Sollmann[15] says that the myoneural junctions paralyzed by atropin are stimulated by pilocarpin. In doses from 1/12 to 1/5 grain hypodermically the contractions are augmented, accompanied by diminished pulse rate. With the change in pulse rate as a criterion for absorption it could be determined that absorption occurred in seven to ten minutes. The contractions were inhibited by subsequent atropin in the usual five to ten minutes. The same effect was noted with section of the nerves, confirming Sollmann's opinion that pilocarpin is effective even after degeneration of the nerves.

Eserin.—Stimulation is produced by eserin, particularly by intravenous administration. In subcutaneous injections there is often a long latent period before activity begins, but activity remains as long as four hours. Again, as with pilocarpin, coincident with the gastric

15. Sollmann: Manual of Pharmacology, 1917, p. 299.

Fig. 2A.—Eserin, 1/60 grain subcutaneously, causing marked contractions last ing an hour and a half.

Figure 2B.

manifestations, in the experiments the pulse rate fell as low as 50 beats per minute, and gradually returned to normal with abolition of the gastric effects. Inasmuch as similar effects were obtained on the "isolated" stomach, the work confirms the belief that eserin also acts on the nerve endings.

TABLE 3.—Eserin

Stomach	Administration	Dose, Grain	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1/60	Contractions	6	1 hr. 30 min.+	For 1 hour contractions unusually strong
Intact	Subcutaneous	1/100	Contractions	6	2 hrs.+	
Intact	Subcutaneous	1/50	Contractions	2	40 min.	Very strong contractions; may have been oncoming regular period
Intact	Subcutaneous	1/60	Contractions			
Intact	Subcutaneous	1/60	No contractions	.....	.....	Administered 19 minutes after atropin 1/60 grain
Intact	Subcutaneous	1/60	Contractions	6	1 hr. 35 min.	Inhibited by atropin
Intact	Subcutaneous	1/100	Contractions	5		
Intact	Subcutaneous	1/80	Contractions	20	30 min.	37 minutes after atropin 1/80 grain
Intact	Subcutaneous	1/80	Contractions	23	4 min.	2 hours 32 minutes after preceding eserin
Intact	Subcutaneous	1/60	Contractions	14	12 min.	39 minutes after preceding eserin
Intact	Intravenous	1/100	Contractions	5	.....	Moderate increase with tonus undulations
Intact	Intravenous	1/100	Contractions	4	.....	Large tonus undulation
"Isolated"	Intravenous	1/100	Contractions	35	.....	Periodic sequence
"Isolated"	Intravenous	1/50	Contractions	7	4 hrs.+	Marked increase
"Isolated"	Subcutaneous	1/40	Contractions	5	.....	Increased tonus
"Isolated"	Subcutaneous	1/40	Contractions	15	2 hrs.+	
"Isolated"	Subcutaneous	1/50	Contractions	5	3 hrs. 15 min.+	
"Isolated"	Subcutaneous	1/40	Slight contractions	20		

Cocain.—In general, it is asserted that cocain first stimulates, then depresses smooth muscle regardless of innervation.[16] Cushny[17] believes that it paralyzes the local nervous mechanism. Profound inhibition occurs with doses of 1 c.c. of 0.5 per cent. solution of cocain per

16. Sollmann: Manual of Pharmacology, 1917, p. 252.
17. Cushny: Pharmacology and Therapeutics, 1913, p. 308.

Fig. 3.—Cocain, 1 c.c. of 1 per cent. per kilogram subcutaneously, causing profound inhibition lasting over two hours.

kilogram. The tracings give a striking picture demonstrating why cocain allays the hunger pangs.

TABLE 4.—Cocain

Stomach	Administration	Dose	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Intravenous	3 c.c. 0.5% 7.8 kg.	Inhibition	1	30 min.+	Lowered tonus; increased respiratory rate
Intact	Subcutaneous	1 c.c. 0.5% per kg.	Inhibition	10	2 hrs.+	Lowered tonus; active period shortened
Intact	Subcutaneous	1 c.c. 0.5% per kg. 14 c.c.	Inhibition	26	1 hr. 30 min.+	Given in active period; preliminary rise in tonus and contractions; then lowered tonus and contractions and increased respirations
Intact	Subcutaneous	0.5 c.c. 1% per kg. 5 c.c.	Slight inhibition	45	1 hr.+	Given in moderately active period; low degree contractions
Intact	Subcutaneous	1 c.c. 1% per kg. 9.2 c.c.	Inhibition	15	2 hrs.+	Marked salivation; animal licking nose
Intact	Subcutaneous	1 c.c. 1% per kg. 8 c.c.	Inhibition	10	2 hrs. 30 min.+	Never regains usual vigorous contractions
Intact	Subcutaneous	1 c.c. 1% per kg. 7 c.c.	Inhibition	.....	.....	Gradually appearing lowered tonus and increased respirations
Intact	Subcutaneous	1 c.c. 1% per kg. 11 c.c.	Inhibition	18	2 hrs.+	Marked result
Intact	Subcutaneous	1 c.c. 1% per kg. 9 c.c.	Inhibition	6	2 hrs.+	Marked result
Intact	Subcutaneous	1 c.c. 1% per kg. 9.2 c.c.	Inhibition	10	2 hrs.+	Marked result
"Isolated"	Subcutaneous	1 c.c. 1% per kg. 11 c.c.	Slight inhibition	15	2 hrs.+	Lowered tonus 15 minutes; active 30 minutes then rest 2 hrs.+
"Isolated"	Subcutaneous	1 c.c. 1% per kg. 11 c.c.	Slight inhibition	.....	.....	Increased tonus at first as if remnant of an active period; then lowered tonus and inhibition
"Isolated"	Subcutaneuos	0.5 c.c. 1% per kg. 5.5 c.c.	Slight inhibition	12	1 hr. 30 min.+	Increased respiration; lowered tonus; later complete inhibition for 1 hour 30 minutes

Camphor.—Camphorated oil was administered to determine whether its stimulating effect on the central nervous system is reflected in any manner in the activity of the stomach. The stimulating effect observed is only obtained when the drug is administered intramuscularly. In large doses the contractions appear to become more frequent and intense, and the period of activity is prolonged.

Strychnin.—As widely employed as strychnin is for its tonic value, there has been no experimental evidence for its supposed gastric effect.

TABLE 5.—CAMPHOR

Stomach	Administration	Dose, Grain	Result	Duration of Effect	Remarks
Intact	Subcutaneous	1	No change	.....	Given at beginning of active period contractions began lasting 1 hour 20 minutes
Intact	Subcutaneous	2	Increased activity	2 hrs.+	Given at beginning of increased tonus; contractions began in 4 minutes and lasted 2 hours +
Intact	Intramuscular	3	No change	.....	Given during rest period and observed for 45 minutes
Intact	Intramuscular	3	Increased and prolonged activity	1 hr.+	Given in active period; contractions became more frequent and intense and period prolonged
Intact	Intramuscular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contractions became more frequent and intense and period prolonged
Intact	Intramuscular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contractions became more frequent and intense and period prolonged
Intact	Intramuscular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contractions became more frequent and intense and period prolonged
"Isolated"	Intramuscular	3	Increased and prolonged activity	2 hrs.+	Given in active period; contractions became more frequent and intense and period prolonged
"Isolated"	Intramuscular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contractions became more frequent and intense and period prolonged
"Isolated"	Intramuscular	3	Contractions	2 hrs.+	Given during rest period; contractions began in 10 minutes, lasting 2 hours +

TABLE 6.—STRYCHNIN

Stomach	Administration	Dose, Grain	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1/60	Contractions	5	3 hrs.	Increased excitability
Intact	Subcutaneous	1/60	Contractions	2	1 hr. 30 min.	Prolonged active period
Intact	Subcutaneous	1/60	Contractions	5	2 hrs.	Moderate but prolonged increase
Intact	Subcutaneous	1/60	Contractions	.....	45 min.	Given in active period; increased contractions but diminished when mild spasms began
Intact	Subcutaneous	1/60	Contractions	15	1 hr.	Moderate increase; diminished when spasms began
Intact	Subcutaneous	1/60	Contractions	5	2 hrs.+	Marked increase; given in active phase
Intace	Subcutaneous	1/90	Contractions	10	1 hr.	Given 1 hour after 1:30,000 epinephrin applied to surface of gastric fistula
Intact	Subcutaneous	1/100	No contraction	.....	.....	Given 1 hour after 1:30,000 epinephrin to nasal mucosa
"Isolated"	Subcutaneous	1/60	Slight contraction	.....	.....	Low grade contractions with no definite active or inactive periods for 2½ hours
"Isolated"	Subcutaneous	1/60	Contractions	.....	1 hr. 30 min.	Given in active period; increased tonus and contractions
"Isolated"	Subcutaneous	1/60	Contractions	6	1 hr. 30 min.	
"Isolated"	Subcutaneous	1/90	Contractions	8	2 hrs.	

It is the usual conception that it increases the tone of the centers regulating the gastro-intestinal tract. With doses of 1/90 to 1/60 grain subcutaneously, stomach tonus was increased, but at the same time the general excitability of the animal was increased so that the increased height of the writing level may have been due to the increased tonus of the abdominal muscles. At the same time, however, there appears to be a definite increase in the hunger contractions themselves. Pollak[18] says that strychnin probably has no effect in ordinary doses given hypodermically. Direct application to Auerbach's ganglia causes stimulation.[19]

TABLE 7.—Amyl Nitrite

Stomach	Administration	Dose, Minims	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Inhalation	10	Temporary inhibition	Immediate	5 min.	Slightly lowered tonus
Intact	Inhalation	10	Temporary inhibition	Immediate	½ min.	
Intact	Inhalation	10	Temporary inhibition	Immediate	½ min.	
Intact	Inhalation	5	Temporary inhibition	Immediate	½ min.	Inhibition while animal struggled against inhaling the drug; but a large contraction; "escaped"
Intact	Inhalation	5	Temporary inhibition	Immediate	.....	Only one of the regularly appearing contractions was inhibited 15 minutes after preceding dose
Intact	Inhalation	5	Temporary inhibition	Immediate	½ min.	
Intact	Inhalation	5	Temporary inhibition	Immediate	½ min.	
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	5 min.	Lowered tonus slowly restored
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	5 min.	Given in active phase; lowered tonus quickly restored
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	.....	Persistent low tonus; no contractions
"Isolated"	Inhalation	5	Temporary inhibition	Immediate		
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	15 min.	Given 55 millimeters after preceding dose
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	4 min.	
"Isolated"	Inhalation	5	Temporary inhibition	Immediate	10 min.	Original tonus very slowly restored

Amyl Nitrite.—Hirschfelder[20] says that systemic administration of nitrites relaxes the constriction produced by lead salts, although this

18. Pollak: Biochem. Centralbl., 1910, **10,** 199.
19. Langley and Magnus: Jour. Physiol., 1905-1906, **33,** 37.
20. Hirschfelder: Jour. Am. Med. Assn., 1915, **65,** 516.

Fig. 4.—Strychnin, 1/60 grain subcutaneously; causing increase in tonus and contractions.

Fig. 5.—Amyl nitrite, 5 minims by inhalation, causing only slight temporary inhibition, as shown between X---X.

treatment for lead colic is not successful. Inhalation of 5-minim pearls often repeated after short intervals causes only a temporary inhibition which disappears as soon as the drug is removed from the nostril. The effect may be psychic, but the contractions which follow are not reduced in frequency, intensity or duration. In animals with the nerves sectioned the same inhibition is observed, but after removal of the drug the tonus remains depressed for a long time, only gradually returning to its original height.

TABLE 8.—EPINEPHRIN

Stomach	Administration	Dose	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Intravenous	1 c.c. 1:10,000	Inhibition	Immediate	1 hr.+	
Intact	Intravenous	1 c.c. 1:10,000	Inhibition	Immediate	1 hr.	
Intact	Intravenous	1 c.c. 1:10,000	Inhibition	1	.....	Also lowered tonus
Intact	Intravenous and subcut.	2 c.c. 1:10,000	Inhibition	8	2 hrs.+	Lowered tonus; later complete inhibition
Intact	Raw surface of fistula	1:30,000	Inhibition	3	2 hrs.+	Lowered tonus
Intact	Nasal mucosa	1:30,000	No effect			
"Isolated"	Subcutaneous	1 c.c. 1:10,000	Lowered tonus	10		
"Isolated"	Intravenous	10 min. 1:10,000	Inhibition	Immediate	40 min.	
"Isolated"	Intravenous	10 min. 1:10,000	Inhibition	1	1 hr.+	
"Isolated"	Intravenous	20 min. 1:15,000	Inhibition	2	1 hr.	
"Isolated"	Intravenous	4 c.c. 1:25,000	Inhibition	5	1 hr.+	Period of tetany preceded inhibition

Epinephrin.—Administration of adrenalin (Parke, Davis & Co.) causes prompt and marked inhibition of the hunger contractions. This action should be expected because of its property of stimulating the nerve endings of the sympathetic system. The consequent stimulation of the splanchnic endings counteracts the augmentatory effects acting through the vagi. Meyer and Gottlieb[21] say that epinephrin by mouth and by hypodermic injection is ineffective, and when given intravenously acts only a few minutes. Our tracings show that the inhibitory effect on the hunger contractions when the drug is given intravenously may last much longer. Enough of a 1 to 30,000 solution was absorbed from the eroded surfaces about the gastric fistula to

21. Meyer and Gottlieb: Text Book, Philadelphia and New York, 1914, p. 188.

cause inhibition. Subcutaneous injection gives a slower response. Inhibition also occurs with the "isolated" stomach, since it is known that the physiologic nerve endings stimulated by epinephrin do not degenerate on section of the nerves, so that the epinephrin effect may persist for weeks.

TABLE 9.—ERGOT

Stomach	Administration	Dose, Ampule	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1	Increased contract	5	1 hr.	Increased tonus undulations
Intact	Intramuscular	1	Marked increase	21	1 hr. 30 min.	Unusual steplike rise with great tonus, short rest, then activity
Intact	Intravenous	½	No effect	.....	.....	Two large contractions, then inhibition followed by active period
Intact	Intravenous	1	Temporary inhibition	1	3 min.	Given in active period; subsequent contractions lowered tonus
Intact	Intravenous	1	Temporary inhibition	1	3 min.	Lowered tonus for 30 minutes; return of contractions for 2 hours +
Intact	Intravenous	1	Temporary inhibition	1	3 min.	Lowered tonus following
"Isolated"	Intravenous	1	Temporary inhibition	1	3 min.	
"Isolated"	Intravenous	1	Contractions	1	1 hr. 30 min.	Almost immediate steplike rise with enormous tonus well sustained
"Isolated"	Intravenous	½	No effect			
"Isolated"	Intravenous	1	Contract	3	2 hrs.+	28 minutes after preceding, followed by steplike rise lasting 2 hours +
	Subcutaneous	1	No effect	.....	.....	Given in midst of active period; contractions followed 1½ hours +

Ergot.—It has been found that intravenous injections of the fluid-extract of ergot causes an increase in the spontaneous movements of the alimentary tract.[22] The motor responsiveness to vagus stimulation was also increased. Later, Meltzer and Githens[23] injected 10 mg. of ergotoxin into rabbits and obtained the same results. Using ampoules of ergot intravenously, we usually obtained a temporary inhibition followed by lowered tonus, although contractions ensued. Intramuscular injection in one instance gave a tremendous steplike rise, with extremely high tonus level, followed by a short rest, and then another active period. The same observation was made on injection of an ampoule intravenously in an "isolated" stomach twenty-eight minutes after a similar injection of one-half ampoule.

22. Meltzer and Auer: Am. Jour. Physiol., 1906, **17,** 143.
23. Meltzer and Githens: Proc. Soc. Exper. Biol. and Med., 1916, **13,** 87.

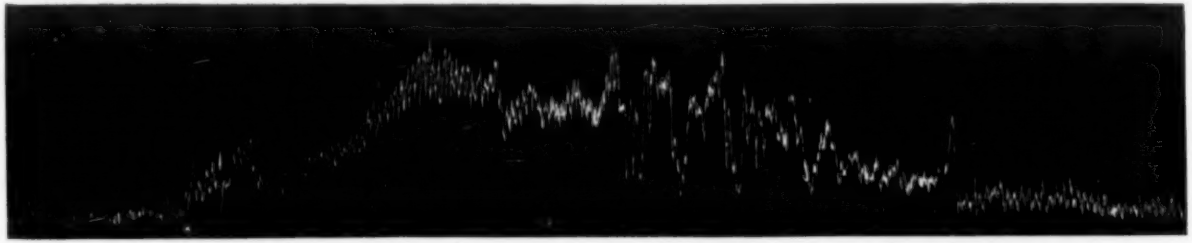

Fig. 6.—Ergot, 1 ampule intravenously, with almost immediate steplike rise, with well-sustained, marked tonus.

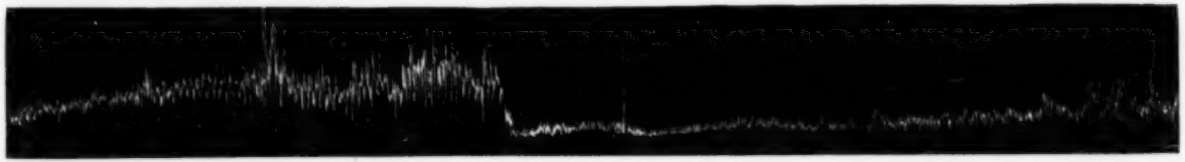

Fig. 7.—Pituitrin (P. D. & Co.), 3 minims intravenously, with prompt inhibition.

Pituitary Extract.—It is commonly believed that pituitary extracts stimulate smooth muscle regardless of innervation, and it is given in paralytic distentions.[24] In the experiments reported the effect of pituitary preparations was remarkably like that of epinephrin. Immediately after injection inhibition occurs. Parke, Davis & Co.'s pituitrin and Armour's pituitary liquid were used with similar results, although

TABLE 10.—PITUITARY EXTRACT

Stomach	Administration	Dose	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1 c.c. (P.D.Co.)	Slight inhibition	7	30 min.+	Given during moderate contractions
Intact	Subcutaneous	1 c.c. (Armour)	No effect	.....	30 min.	Given in quiescent period
Intact	Intravenous	1 c.c. (P.D.Co.)	Inhibition	Almost Immediate	30 min.+	
Intact	Intravenous	5 min. (P.D.Co.)	Inhibition	Almost Immediate	1 hr.	
Intact	Intravenous	3 min. (P.D.Co.)	Inhibition	Almost Immediate	30 min.+	
Intact	Intravenous	0.5 c.c. (Armour)	Inhibition	Almost Immediate	30 min.	After 30 minutes slowly developing contractions appeared
Intact	Intravenous	1.0 c.c. (Armour)	Inhibition	Almost Immediate	1 hr.	Occasional low grade contractions appeared
"Isolated"	Subcutaneous	1.0 c.c. (Armour)	No effect	.....	.....	Given in an active period
"Isolated"	Subcutaneous	1.0 c.c. (P.D.Co.)	Inhibition	16	.....	Given in an active period
"Isolated"	Intravenous	1.0 c.c. (Armour)	No inhibition	.....	.....	Periodic contractions although infrequent, occurred after administration
"Isolated"	Intravenous	1.0 c.c. (P.D.Co.)	Inhibition	Almost Immediate	1 hr.	Subsequent active period short
"Isolated"	Intravenous	10 min. (P.D.Co.)	Inhibition	Almost Immediate	2 hrs.	Given in middle of active period
"Isolated"	Intravenous	5 min. (P.D.Co.)	Inhibition	Almost Immediate	1 hr.	Given in beginning of active period

both preparations caused a rise in blood pressure when tested on crucial animals. In accordance with these results are the results of Bayer and Peter,[25] who noted that pituitrin and also fresh extract of the pituitary body might inhibit the movements and tone of rabbits' isolated intestinal loop. Shamoff[26] and Hoskins[27] found that the intes-

24. Sollmann: Manual of Pharmacology, 1917, p. 339.
25. Bayer and Peter: Arch. f. exper. Path. u. Pharmakol., 1911, **64,** 209.
26. Am. Jour. Physiol., 1915-1916, **39,** 268.

tinal action varies greatly in different preparations, some even relaxing like epinephrin. Even extracts of fresh glands gave this result, although blood pressure tests were normal. The effects of pituitrin were remarkable in their inhibitory effects. Having determined the length of the periods by mere recording without administering the drug, one could observe that administration of pituitrin cut short the active period so that the subsequent rest period equaled the rest period usual for that animal on that particular day plus the "inhibited" portion of the previous active period arrested by pituitrin. By repeating the drug one could predict with surprising accuracy about the time of onset of the next active period. It appears, therefore, that the action of pituitrin is of short duration.

COMMENT

To preserve the conditions of experimentation as nearly constant as possible the records were taken about 1 p. m., running on until about 5 p. m. The dogs were then fed and given nothing else but water until after the next observation at the same hour on the next day. To obtain more accurate results the drugs were given by routes enabling prompt absorption and action so that the change in the picture of gastric motility might be referred to the manipulation. Observations were made for some time before injections to determine whether the stomach was in a period of rest or activity. Only in this way, recording several periods, can the observer decide that he is dealing with the beginning of a rest or active period as the case may be. By observing the periodicity the time interval may be determined so that one may conclude fairly regarding the effects of the drug. For instance, if a drug is administered at the end of an active period the subsequent rest period may be fallaciously ascribed to the drug. In any work involving the hunger contractions it is of prime importance to determine the phase of gastric motility and repeat the manipulation during different phases. There still remains a large field for intensive experimentation with drugs by varying the preparations and dosages, studying the intestinal movements simultaneously and checking results with observations on the other pharmacologic effects of the drug employed, which the exigencies of the present situation prevent the authors from surveying.

Thanks are due Drs. A. J. Carlson and A. B. Luckhardt for their valuable suggestions and Dr. Jacob Meyer and Mr. Seymour Cohen for their kind assistance in part of the work.

27. Hoskins: Jour. Am. Med. Assn., 1916, **66**, 732.

REPORT OF A CASE OF PAROXYSMAL TACHYCARDIA CHARACTERIZED BY UNUSUAL CONTROL OF THE FAST RHYTHM*

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In view of the fact that the subject of this report possessed to a remarkable degree the power of control over his pathologic rhythm, the following instance of paroxysmal tachycardia in a young adult seemed to us of sufficient interest to report in some detail. It is greatly to be regretted that we had but a single opportunity to observe the individual for a few hours, as he left the city permanently the day after these observations were recorded.

Apart from the control of these ectopic rhythms occasionally seen following vagus stimulation either by direct pressure or reflexly as a result of various methods of clinical procedure, their voluntary control is seldom met with.

Although it is impossible in the present instance to determine with absolute exactness the means by which such voluntary inhibition is exercised, we have assumed that our use of the term "voluntary control" implies essentially the power on the part of the individual to bring about an abrupt change in his cardiac rate that is undoubtedly induced by some indirect vagal stimulation.

The subject of this note had for many years experienced attacks of abrupt, extreme acceleration of his cardiac rate, brought on at widely varying intervals by some unusual slight exertion, or often without any definitely known exciting cause, these attacks always being accompanied by the usual symptoms of distress referable to his disturbed circulation. Four or five years previously he first noticed that he had acquired the power to cut short these attacks, as he expressed it, by voluntary effort. This was accomplished apparently by a mental concentration associated frequently with an effort to yawn, or by a forced deep inspiration momentarily held.

When seen in September, 1917, by one of us, he seemed to have the power of initiating the onset of his tachycardia in much the same

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* From the Medical Clinic of the Cleveland City Hospital and the Western Reserve University.

way that he now controls its offset, without any evident muscular effort. As, however, satisfactory records were not obtained at this time we cannot say definitely that this was a correct interpretation.

At present, February, 1918, he can induce the onset of his fast rhythm by various slight abrupt muscular efforts, but no similar effort had the slightest effect in controlling the offset of the new rhythm, this being accomplished solely by some conscious subjective effort while sitting quietly with his hands and foot in the immersion electrodes. Neither yawning nor any disturbance of his respiratory rhythm alone was sufficient to abort the attack, some other factor seeming to be necessary.

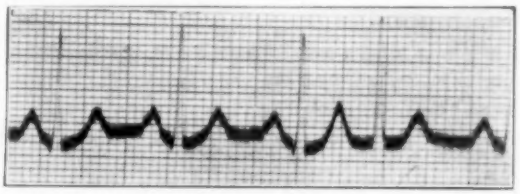

Fig. 1.—Normal electrocardiogram. Lead II. Rate 108 per minute. The P-R interval measures 0.15 second. Note the premature atrial systole.

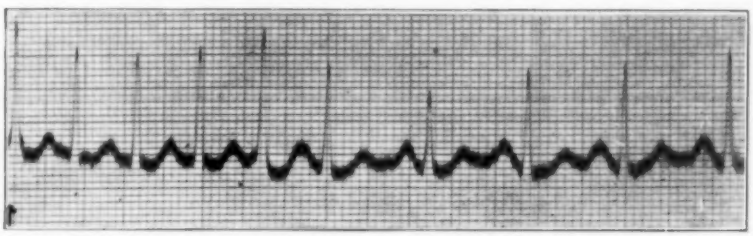

Fig. 2.—Lead II. First half of the figure during the pathologic tachycardia, rate 200 per minute. At the point marked by the arrow he was asked to stop the paroxysm. The change from the fast to the slow rate is apparent, in this instance, without any long pause. The P-R interval measures 0.15 second. Note the marked inequality in the height of the R peaks, and with the onset of the slow rate the very suggestive "staircase" phenomenon.

His history is briefly as follows:

F. P. L.,[1] aged 29, student, a Russian Jew. The family history was negative.

Personal History.—There was no history of rheumatic fever, scarlet fever or diphtheria. He had an acute short attack of influenza in 1912, but no history of any other illness. He denied any venereal infection. He had used alcohol and tobacco in moderation. He thought smoking increased the frequency of the attacks and at one time stopped smoking for nine months, but noticed no material improvement.

1. We are indebted to Dr. Harold Feil for the opportunity to observe this patient.

Present Illness.—Occurrence of attacks of sudden acceleration of his heart rate dated from 1905, when 17 years of age. These attacks lasted from a few minutes to twelve hours, the longer ones always accompanied by a sense of fulness and distress in the head. These attacks commonly followed some unusual though slight muscular effort and were much more apt to occur if he missed his midday meal or at any time if he felt hungry.

Physical Examination.—The man was of slight frame, fairly well nourished; muscular development slight; no pathologic deformities noted. The upper border of cardiac dulness was at the third interspace; the point of maximum impulse 10 cm. from the midsternal line in the fifth interspace; right border at the right sternal edge; heart sounds clear; first sound at the apex slightly accentuated with every fourth or fifth systole; no murmurs heard; pulse apparently regular in rate and volume, though varying between the two slow rhythms 85 and 106 at different times. Blood pressure 112 and 80. The man gave one the impression of being a very high strung individual with an unstable nervous balance so characteristic of his race.

ANALYSIS OF THE ELECTROCARDIOGRAMS

In a detailed study of the figures accompanying this report, and additional similar records not reproduced, a number of interesting facts are apparent.

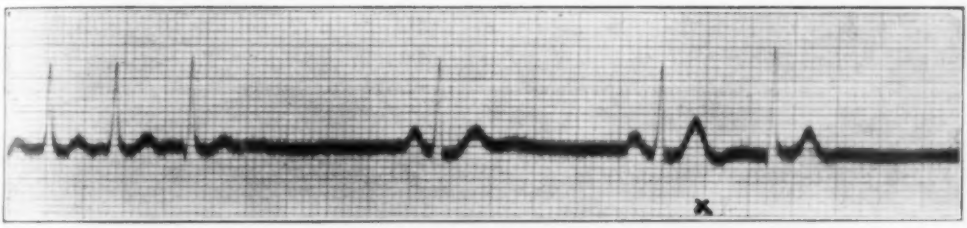

Fig. 3.—Lead II. Fast rate 200. At a point three cycles to the left of the first cycle of this figure he was asked to stop the tachycardia. Note the abrupt change to the slow rate. The last P-R interval before the first long pause is slightly increased. The R-R interval of the first long pause measures 1.20 seconds, the R-R interval of the second pause measures 1.04 seconds. The P-R interval with the long pauses measures 0.16 second, that with the premature systole at x measures 0.320 second.

The dominant rate of the pathologic rhythm remained constantly at approximately 200 per minute, varying between 196 and 204, a rate that, according to Lewis,[2] approaches the borderline in the arbitrary classification between a true paroxysmal tachycardia and atrial flutter. As a simpler and more logical distinction between these two forms of tachycardia, we have considered that the failure of ventricular response, in the presence of these borderline speeds, constituted the essential distinguishing difference, a distinction endorsed by Hart,[3]

2. Lewis: Clinical Electrocardiography, Shaw & Sons, London, 1913.
3. Hart: Abnormalities of Myocardial Function, The Rebman Co., New York, 1917.

who further places the arbitrary difference in rate between the two at the still higher atrial speed of 250 per minute. In none of our records, however, was there at any time a failure of ventricular response during the presence of the atrial tachycardia.

THE VENTRICULAR COMPLEX

At times, but only for short intervals, the cardiac rate slowed down to 85 per minute, the dominant slow rate ranging between 106 and 108, with a normal electrocardiogram in all three leads and with a normal conduction time. The form of the ventricular complex remains the same at all speeds of the heart before, during and after atropin, showing no pathologic alteration except the alternation noted later.

In the presence of the pathologic tachycardia it is possible that confusion might arise in an analysis of the galvanometric curves as to the presence of a negative P-wave with a lengthened conduction time, were the evidence always as suggestive as is seen in the distinctly negative deflection of the string following R in Figure 9. Elsewhere

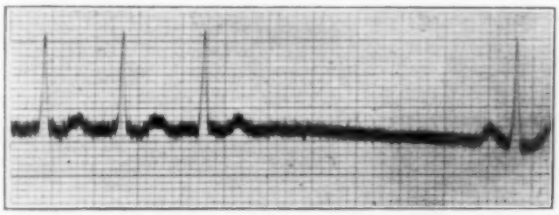

Fig. 4.—Lead II. Abrupt stoppage of the fast rate. Signal given four cycles to the left of the first cycle of the figure. R-R interval measures 1.42 seconds.

in all our records there was no such suggestive negative deflection, and we have assumed that T and P are fused, P appearing as a positive wave, as is so evident with the occurrence of isolated premature atrial contractions.

In all the records of our series there is a conspicuous variation in the height of the R peaks, amounting in many instances to a definite alternation. In Figure 2, illustrating the first recorded transition from the fast to the slow rate, the first four cycles of the slow rhythm show a very suggestive "staircase" phenomenon, which may be looked on as additional evidence of a vagus reflex.[4]

THE P-R INTERVAL

With the onset of the fast rhythm the P-R interval remains practically unchanged. With the abrupt offset of the pathologic tachy-

4. Vinis: Heart, 1912, **4**, No. 2, p. 123. Ritchie: Quart. Jour. Med., 1912, **6**, No. 21, p. 47.

cardia to the slower rate of 106 following voluntary effort, there is but a slight change in the conduction time preceding the transition, the P-R interval lengthening for the last cycle of the fast rate to shorten again with the establishment of the slower rhythm after the pause.

When, however, he was able to slow the dominant rate of 106 down to 85 per minute, the transition was invariably accompanied by a conspicuous lengthening of the P-R interval, associated with an isolated extrasystole of atrial origin, followed by a long pause (Fig. 8). At x (Fig. 8) the P-R interval measures 0.28 sec. In another similar instance it was increased to 0.30 sec.

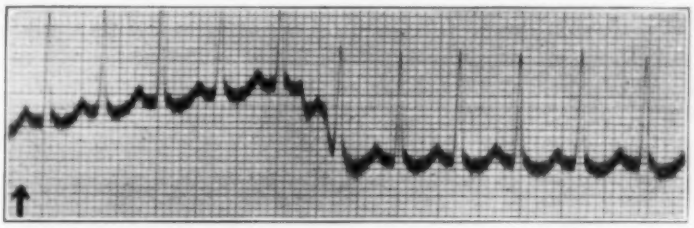

Fig. 5.—Lead II. Rate 200. Right vagus stimulation during the tachycardia. Vagus pressure applied at point marked by arrow. No change in rate.

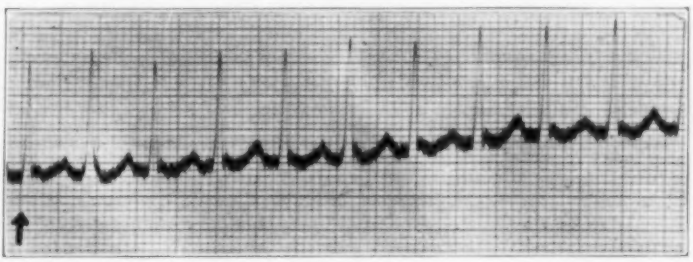

Fig. 6.—Lead II. Rate 200. Left vagus stimulation during the tachycardia. Vagus pressure applied at the point marked by arrow. No change in rate.

The P-R interval then measures 0.16 sec. during the slowest rate of 85, the dominant slow rate of 106, in the presence of the pathologic cardia to the slower rate of 106 following voluntary effort, there is tachycardia and in the escape under atropin, only lengthening conspicuously, as is to be expected, with the transition from a fast to a slower rate.

EFFECT OF MECHANICAL VAGUS STIMULATION

Repeated attempts by pressure applied over both the right and left vagus failed utterly to induce the slightest change in either the rate or the cardiac rhythm. This failure to demonstrate any alteration in the cardiac response to mechanical stimulation of the vagi seems

curiously inconsistent with the results that one would have expected in an instance of the sort under consideration. That in many instances of paroxysmal tachycardia vagal stimulation is without the slightest effect is too well known to need comment, but just how to reconcile the man's own power of subjective control over his fast rhythm, so evidently of vagal origin, in the face of our failure to influence it in the slightest by vagal pressure, is not so simple.

Cohn and Fraser,[5] in a study of paroxysmal tachycardia and the effect of vagus pressure, suggest that when vagal stimulation by pressure fails to control the paroxysmal attack and other methods succeed, the results may well be attributed to the stimulation of the inhibitory mechanism by the successful procedure and failure to do so by all other methods, an explanation that is after all not wholly satisfactory.

In a study of certain cases of rhythmic irregularities Robinson and Draper[6] regarded the inability to produce any change in the

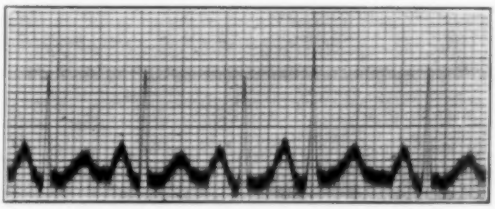

Fig. 7.—Lead II. Twenty-five minutes after 1.3 mg. of atropin. Rate 144 per minute. Fifteen minutes after atropin, rate 135; an hour after atropin, rate 120. Two hours after atropin the heart had escaped from atropin effect. Note the alternation.

cardiac rhythm by vagal pressure as due to an increased vagal tone; the heart in one case described by them escaping under atropin and attaining a rate greatly in excess of the rhythmic tachycardia, when the individual was no longer able to induce the changes in rhythm brought about by deep forced inspiration. They conclude that in this case the vagus tone "controlled a heart which would otherwise have beat at an abnormally rapid rate."

In this connection the experimental observations of Rothberger and Winterberg[7] on the influence of the vagus and accelerator nerves on the galvanometric curves from the dog's heart are of interest. These observers were able to show that in the experimental animal stimulation of the vagus and accelerator yielded curves essentially the

5. Cohn and Fraser: Heart, 1913, **5,** No. 1, p. 93.
6. Robinson and Draper: Heart, 1912, **4,** p. 97.
7. Rothberger and Winterberg: Centralbl. f. Physiol., 1910, **24,** 790. idem., Pfluger's Arch. f. d. ges. Physiol., 1910, **135,** 506.

antithesis of each other; vagus stimulation giving a low voltage P and T with a conspicuous R deflection, while stimulation of the sympathetic gave a lower R with conspicuous P and T waves. There are admittedly many difficulties in applying the experimental evidence in this connection too dogmatically to the clinical picture, and yet in those instances in which the cardio-inhibitory or accelerator influence is definitely subject to marked voluntary control the suggestive comparison of the experimental and clinical galvanometric curves should not be lost sight of.

Flavell and White,[8] in reporting a case of voluntary acceleration of the cardiac rate not associated with any apparent change of the pacemaker, referring to the observations of Lewis and Cotton[9] say that "the changes in the electrocardiographic deflections during the acceleration are those which are known to occur when the sympathetic is stimulated experimentally." Further, as evidence that the voluntary increase of the heart rate is the result, in great part at least, of the

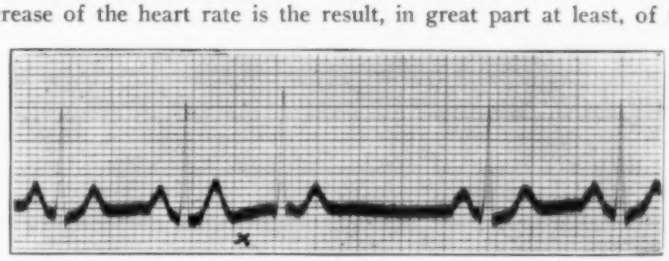

Fig. 8.—Lead II. After escape from atropin effect. Note the voluntary control of the slow rate. First half of figure, rate 108; second half following the long pause, 86 per minute. The P-R interval measures 0.16 second for the first three cycles. With the extrasystole at x the P-R interval measures 0.26 second. The R-R interval following the extrasystole measures 0.96 second. The P-R interval of the next cycle measures 0.14 second and then reverts to 0.16 second.

action of the accelerator mechanism, they cite the fact that "the escape under atropin in large doses produces not one-half of the increase in pulse rate that results from voluntary acceleration." A fact, however, of even greater significance, it seems to us, in the case reported by Flavell and White, is the ability on the part of the subject of their note to break through the rate under the escape from atropin and induce a higher rate, an ability not possessed by the subject of this report.

In discussing this question as to why stimulation of the vagi by pressure is effectual in some cases of paroxysmal tachycardia and not

8. Flavell and White: Heart, 1917, **6,** No. 3, p. 175.
9. Lewis and Cotton: Proc. Phys. Soc., June 28, 1913.
10. Robinson, G. C.: The Archives Int. Med., 1915, **16,** 967.

in others, Robinson[10] says that it seems probable that this difference is due to the character of the cardiac derangement responsible for the tachycardia, depending on the anatomic relation between the distribution of the vagi and the point taking up the rôle of hyperactive pacemaker. This conclusion, so readily applicable in many instances, does not, however, aid in the explanation of the failure of vagal pressure to control the fast rate in our case, which seems so curiously paradoxical.

ESCAPE UNDER ATROPIN

Following 1.3 mg. of atropin the ventricular escape reached as its highest rate, 144 per minute (Fig. 7). The degree of ventricular escape amounted to approximately the average normal figure, being on the basis of the dominant rate, an increase of 35 per cent.

We have not assumed that the mere removal of vagal control in this instance would *per se* tend to increase the incidence of the paroxysmal attacks, but because of the very evident subjective control over the pathologic tachycardia, and in spite of the fact that it was constantly so uniformly rapid, we hoped that under the influence of atropin it might be possible to induce the pathologic rhythm with even greater facility than before its administration. While under the influence of atropin, however, he was utterly unable to break through the rate due to the cardiac escape and induce the higher speed of the ectopic rhythm. That all inhibitory vagal control had been removed was evidenced by the utter failure to control subjectively the rate under atropin, and by the conspicuous physiologic effects of the drug. Had the pathologic tachycardia been of a lower rate than that under the escape following atropin, the explanation for the failure to induce the ectopic rhythm after removal of vagal tone would be less difficult. That, however, the administration of atropin or belladonna in some form over a variable period of time to persons subject to attacks of paroxysmal tachycardia does not increase the incidence of such attacks is also a matter of observation.

The reaction to atropin in this case is further proof that we were not dealing with an ectopic focus wholly removed from neurogenic control as in the high speed atrial rate of true flutter. Following partial recovery from the atropin effect, two hours after its administration, he was again able to induce the pathologic rhythm and could again retard his slow rate of 106 down to 85 per minute (Figs. 8 and 9).

THE INCIDENCE OF PREMATURE CONTRACTIONS

As is to be expected, the incidence of single premature atrial contractions increased with the slower rates, disappearing entirely in the presence of the tachycardia. But of greater interest is the fact that

they do not disappear entirely under atropin, evidence, we consider, of definite pathologic significance. When these occur, as in Figure 1, free from any conscious effort on the part of the individual to slow his heart, the atrial pause is less than compensatory by 0.16 sec. Under the influence of conscious effort to slow the cardiac rate, as in Figure 8, the atrial pause is greatly increased, being overcompensated by 0.26 sec. There is, further, a curiously constant relationship in the time of the appearance of the atrial extrasystole to the preceding ventricular complex. Extra systoles of ventricular origin were at no time recorded.

VOLUNTARY CONTROL OF THE TACHYCARDIA

In every instance when asked to stop the pathologic tachycardia the result was accomplished within a few cycles of the command, and in every record but one (Fig. 2) the transition occurred with one or more long pauses during which the R-R interval measures all the way from 0.96 sec. to 1.42 sec. The pause involved a complete standstill of the

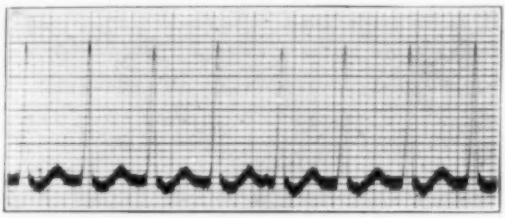

Fig. 9.—Lead II. Rate 200. After the escape from atropin effect. The pathologic tachycardia. Note the alternation and the very suggestive negativity of the string following the R-complex. See reference in text.

heart and frequently measured more than twice the R-R interval of the dominant rhythm of 106 to the minute. In Figure 4 it exceeds even twice the R-R interval of the slowest rate of 86 to the minute. This fact, together with the lengthening of the P-R interval that invariably accompanied isolated premature systoles, points to the predominant effect of vagus control in cutting short the fast rhythm and in slowing down the predominant slow rate of 106 to 85. That the abeyance of vagus control had not the slightest influence in inducing the paroxysmal rhythm seems as equally well established as is the evidence of the man's voluntary control over his inhibitory mechanism.

When asked to cut short the paroxysmal attack while connected with the galvanometer it was interesting to watch his method of procedure. He closed his eyes, inclined his head backward and slightly to the left and then would apparently concentrate his mind on the effort to check the tachycardia without any visible change in the respiratory rate.

SUMMARY

In view of the constant similarity of the ventricular complex, the constancy of the conduction time, except during the transition from a higher to a lower rate, together with the constant time relationship of the extrasystoles to the preceding ventricular contraction and the direction of the P-wave, we have assumed that we were dealing with an ectopic rhythm originating in the upper level of the atrium near the pacemaker, conspicuously under the control of subjective inhibitory reflexes, but utterly uninfluenced by vagal stimulation.

There is no demonstrable evidence of any accelerator influence or control over the tachycardia, in spite of the general inferences supporting such a view and the similarity of the ventricular complexes to the experimental observations alluded to.

REMARKS ON THE CONCENTRATION OF UREA IN HUMAN BLOOD*

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The majority of investigators who have studied the problem of kidney function, particularly in relation to impaired elimination, accord increasing importance to the estimation of nitrogenous substances in the blood. Though the relation of nitrogen retention in the blood to the pre-uremic and uremic manifestations in the clinical picture of nephritis is not sufficiently understood to allow definite interpretation as to diagnosis and prognosis, there can be no doubt that nitrogen retention is intricately connected with disturbances arising from impaired kidney function.

Among the nitrogenous substances of the blood, urea has received particular attention for a number of reasons which need not be analyzed here. As a result of many careful investigations, the retention of urea in the blood is now generally regarded as a reliable diagnostic sign of faulty kidney function; but, on the other hand, there still remains a disturbing degree of confusion as to what should be considered the normal and what a pathologic urea content of the blood.

The concentration of urea in the blood of healthy adults has been the subject of numerous investigations, the more important of which are summarized in Table 1.

Of the investigators listed here, Folin and Denis,[1] Tileston and Comfort,[2] and Myers and Killian,[3] all find practically the same narrow range of normal values. On the other hand, McLean and Selling,[4] Gettler and Baker,[5] and Addis and Watanabe,[6] find a very much wider range of normal values, and Schwartz and M'Gill[7] are unique in that the highest value in their series of normals is practically identical with the low limit of the normal range as determined by other investigators. This fact seems to have been overlooked by other workers, for Schwartz and M'Gill are frequently quoted as finding from 10.8 to 25.2 mg. of urea nitrogen per 100 c.c. of blood, whereas they actually

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1. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29.
2. Tileston, W., and Comfort, C. W.: THE ARCHIVES INT. MED., 1914, **14,** 620.
3. Myers, V. C., and Killian, J. A.: Jour. Biol. Chem., 1917, **29,** 179.
4. McLean, F. C., and Selling, L.: Jour. Biol. Chem., 1914, **19,** 31.
5. Gettler, A. O., and Baker, W.: Jour. Biol. Chem., 1916, **25,** 211.
6. Addis, T., and Watanabe, G.: THE ARCHIVES INT. MED., 1917, **19,** 507.
7. Schwartz, H., and M'Gill, C.: THE ARCHIVES INT. MED., 1916, **17,** 42.

report 10.8 to 25.2 mg. of urea per 100 c.c. of blood. Moreover, these extremely low figures are reported as the urea content of specimens taken "two and one-half hours after a heavy protein meal," a time when the urea concentration of the blood would naturally be somewhat increased as a result of the processes of absorption and assimilation. On the whole, the evidence for a wide range of normal values is far from convincing; the concentration of urea nitrogen in the blood of normal, healthy adults seems to lie between 12 and 15 mg. per 100 c.c.

TABLE 1.—Concentration of Urea Nitrogen in Normal Human Blood

Investigators	Number of Subjects	Urea N of Blood, Mg. per 100 C.c.	Remarks
Folin and Denis[1]	16	11 to 13	Three to six hours after breakfast
Schwartz and M'Gill[7]	4	5 to 7.1	After seventeen hours' fast
Schwartz and M'Gill[7]	15	5 to 11.7	Two and one-half hours after a "heavy protein meal"
Addis and Watanabe[6]	22	10.5 to 28	Before breakfast; 106 determinations on twenty-two subjects
Gettler and Baker[5]	30	15 to 25	Three hours after a standard breakfast
Tileston and Comfort[2]	5	12 to 14.1	After twelve hours' fast
Tileston and Comfort[2]	..	13.1 to 20.9	Two and one-half hours after an average meal
Myers and Killian[3]	6	12 to 15	Before breakfast
McLean and Selling[4]	..	10 to 23	Under varying conditions

Assuming the accuracy of these narrow limits as repeatedly confirmed by the observations of Folin and his collaborators, and of various workers in our own laboratories, we are still confronted with the question, Is the normal concentration of urea in the blood of hospital patients without evidence of kidney lesion the same as that of healthy individuals, and is the normal sharply differentiated from the pathologic?

In the hope of answering these questions we have made the following study of 298 routine analyses of the blood of 244 patients treated in our own medical wards. This special series was selected for investigation because it includes the analysis of at least one specimen from each patient in the wards during a period of five months, and for that reason seems to offer a fairer criterion of urea values than would a study of carefully selected groups of typical cases. All specimens examined in which the urea nitrogen exceeded 35 mg. per 100 c.c., were from patients unquestionably nephritic; for this reason the series discussed here includes only those cases in which the urea nitrogen was less than 35 mg. per 100 c.c.

In order to obtain specimens of which the urea content is justly comparable, two variable factors must be guarded against: (1) during

the processes of digestion and absorption, the increase in concentration of blood urea depends partly on the nature of the food intake, and (2) this increase is of a more lasting nature in persons with impaired renal excretory powers than in healthy persons. We have, therefore, adopted the practice of taking all blood specimens before

TABLE 2.—CASES WITH UREA NITROGEN OF LESS THAN 12 MG. PER 100 C.C. OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
1. J. C.	50	♀	10.8	Duodenal ulcer	
2. A. G.	12	♀	10.5	Duodenal ulcer	
3. D. T.	30	♂	10.8	Gastric ulcer	
4. M. C.	55	♀	11.6	Typhoid	
5. B. G.	21	♀	10.8	Typhoid	Occasional cast
6. E. P.	23	♀	11.6	Spastic colitis; adhesions	
7. R. K.	23	♀	10.1	Spastic colitis	
8. H. D.	21	♂	11.6	Chronic endocarditis	
9. J. L.	19	♀	11.1	Chronic endocarditis; myocarditis	Faint trace of albumin
10. G. G.	55	♂	11.6	Chronic endocarditis	
11. M. B.	30	♂	11.6	Huntington's chorea	
12. P. K.	25	♀	11.6	Neurasthenia	
13. S. W.	60	♂	11.1	Pyloric obstruction; duodenal ulcer	
14. T. M.	23	♂	11.1	Chronic constipation	Phthalein, 19 per cent.
15. N. F.	45	♀	11.1	Chronic constipation; colitis	
16. V. F.	34	♂	10.8	Auricular fibrillation	Faint trace of albumin
17. N. F.	65	♀	10.8	Diabetes mellitus	Occasional cast
18. V. S.	18	♂	11.6	Meningitis	
19. J. H.	20	♂	10.8	Lobar pneumonia	
20. M. C.	22	♀	9.8 10.1	Undeveloped, retroverted uterus	Phthalein, 30 per cent., 34 per cent.
21. J. E.	54	♀	11.6	Calloused ulcer of pylorus	
22. J. W.	51	♂	11.6	Retroperitoneal sarcoma	Phthalein, 26 per cent.
23. R. K.	36	♀	9.0	Chronic endocarditis; auricular fibrillation	
24. J. S.	38	♂	10.5	Hypertension; thrombosis of central vein of left eye	Blood pressure, 165/100
25. F. S.	35	♀	11.1	Enteroptosis	Phthalein, 36 per cent.
26. M. B.	39	♀	11.1	Enteroptosis	
27. I. G.	50	♂	10.8	Chronic parenchymatous nephritis	Trace of albumin
28. S. R.	29	♀	11.6	Parenchymatous nephritis, hemorrhagic	Moderate amount of albumin; occasional cast
29. S. F.	35	♀	11.1	Gastritis and gastralgia	
30. M. B.	35	♀	10.5	Carcinoma of sigmoid and liver	
31. C. R.	24	♀	11.1	Lymphosarcoma	

TABLE 3.—Cases with Urea Nitrogen of 12.1-15 Mg. Per 100 C.c. of Blood

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
32. H. C.	24	♂	13.5	Lobar pneumonia	Blood sugar, 0.171 per cent.
33. C. E.	29	♂	13.5	Lobar pneumonia	Blood sugar, 0.168 per cent.
34. D. B.	16	♀	12.6	Lobar pneumonia	
35. N. S.	24	♂	13.0	Lobar pneumonia	Blood sugar, 0.177 per cent.
36. M. W.	25	♀	13.5 13.0	Bronchial pneumonia	
37. Y. B.	19	♀	13.5	Pleurisy; pneumonia	
38. M. G.	25	♀	12.6	Pleurisy, with effusion	Phthalein, 22 per cent.
39. D. R.	30	♂	9.3 14.1	Pleurisy	Faint trace of albumin
40. C. J.	31	♂	12.6	Chronic gout	Creatinin, 3.5 mg. per 100 c.c.
41. H. S.	31	♂	14.5	Gas poisoning	
42. G. H.	68	♂	14.5	Chronic arthritis	
43. A. W.	10	♀	13.5 12.3	Chronic arthritis	
44. H. M.	41	♀	12.6	Chronic arthritis	
45. A. B.	52	♂	14.5	Chronic arthritis	Blood pressure. 170/100
46. E. T.	45	♀	12.0	Acute septic arthritis	
47. L. S.	27	♀	12.3	Pulmonary tuberculosis	
48. E. K.	42	♀	12.0	Pulmonary tuberculosis	Phthalein, 34 per cent.; blood pressure, 215/115; faint trace of albumin
49. J. S.	18	♂	13.0	Incipient tuberculosis	Moderate number of casts
50. M. G.	30	♀	13.8	Incipient tuberculosis	
51. J. F.	17	♂	13.7	Tuberculosis of left kidney	Trace of albumin
52. A. A.	49	♀	12.0	Tuberculosis; keratitis	
53. A. B.	41	♂	12.6	Aortitis	
54. H. K.	10	♂	12.6	Spastic colitis	Occasional cast
55. M. M.	58	♂	12.6	Spastic colitis	Phthalein, 10, 24, 17 per cent.
56. J. S.	28	♂	14.1	Spastic colitis	
57. B. L.	40	♀	14.1	Myocarditis	Blood sugar, 0.177 per cent.; faint trace of albumin; phthalein, 22 per cent.; blood pressure, 155/125
58. J. V.	33	♂	13.8	Myocarditis	
59. T. C.	51	♂	13.1	Myocarditis	Occasional cast
60 B. G.	47	♀	12.6	Myocarditis	
61. E. B.	44	♂	12.5	Myocarditis	
62. L. R.	61	♀	13.8	Hysteria	
63. R. M.	14	♂	14.8	Tetanus	
64. M. D.	23	♀	12.6	Arteriosclerosis; hypertension	Trace of albumin
65. M. Y.	66	♂	13.6	Arteriosclerosis; aortitis	Moderate amount of albumin; phthalein, 29 per cent.
66. C. H.	44	♂	12.6	Lues; general paresis	
67. L. N.	36	♀	14.1	Lues	Faint trace of albumin
68. G. L.	50	♂	14.5	Paresis	

TABLE 3.—CASES WITH UREA NITROGEN OF 12.1-15 MG. PER 100 C.C. OF BLOOD—(*Continued*)

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
69. F. B.	35	♂	12.8	Paresis	Phthalein, 27 per cent.
70. S. M.	28	♂	13.5	Syphilis; progressive muscular atrophy	
71. G. R.	24	♀	13.5	Typhoid	
72. E. G.	13	♀	12.3	Typhoid	
73. B. B.	23	♀	12.6	Gastric ulcer	
74. H. M.	44	♂	12.6	Gastric ulcer	
75. J. K.	36	♂	12.3	Gastritis	
76. J. H.	63	♂	13.5	Carcinoma of stomach	Trace of albumin; moderate number casts; creatinin 3.5
77. M. P.	33	♀	12.3	Autointoxication	
78. M. S.	23	♂	12.3	Psychasthenia	Occasional cast; faint trace of albumin
79. Y. F.	33	♀	13.0	Subacute gastro-enteritis	Creatinin, 3.5 mg. per 100 c.c.
80. J. V.	31	♂	13.8	Pontine neoplasm	
81. L. S.	13	♂	13.0	Malaria	
82. Y. S.	21	♀	13.8	Atrophy of eyeball	
83. L. L.	8	♂	12.6	Tonsillitis	
84. B. H.	52	♀	13.0	Pyorrhea; leukorrhea	
85. L. Z.	21	♀	14.5	Hysterical epilepsy	Faint trace of albumin
86. C. M.	55	♂	13.0	Atrophic cirrhosis of liver; ascites, pleural effusion	
87. A. F.	27	♂	12.6	Hypertrophic cirrhosis of liver	
88. M. F.	50	♀	14.5	Abdominal tumor of spleen; syphilis	
89. H. B.	38	♀	14.1	Chronic hypertension; neurasthenia	
90. H. C.	25	♀	13.5	Spinal lesions	
91. E. M.	27	♂	14.8	Streptococcus septicemia; chronic endocarditis	
92. D. T.	55	♂	14.8	Chronic appendicitis	Occasional cast
93. S. C.	48	♂	14.5	Chronic appendicitis	
94. F. L.	29	♀	14.5	Chronic constipation and appendicitis	
95. M. H.	43	♂	14.8	Pulmonary abscess	
96. A. C.	54	♀	12.0	Chronic endocarditis; general carcinomatosis	
97. M. B.	52	♀	14.8	Endocarditis	Blood sugar, 0.192 per cent.
98. G. T.	31	♀	13.5	Endocarditis	
99. D. M.	19	♂	12.6	Malignant endocarditis	
100. C. B.	18	♂	14.5	Chronic endocarditis, mitral regurgitation and stenosis	
101. F. G.	63	♀	12.0	Diabetes mellitus	Occasional cast; blood sugar, 0.168 per cent.
102. I. G.	60	♀	14.0	Diabetes mellitus	

TABLE 3.—Cases with Urea Nitrogen of 12.1-15 Mg. Per 100 C.c. of Blood—(*Continued*)

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
103. W. P.	43	♂	13.5	Diabetes mellitus	Blood sugar, 0.228 per cent.
104. R. V.	19	♀	15.0	Diabetes mellitus	
105. J. M.	56	♂	13.5	Diabetes carcinoma of liver	Blood sugar, 0.280 per cent.
106. A. L.	34	♀	13.0	Chronic endometritis and appendicitis	
107. H. S.	46	♂	13.5	Neuritis	
108. J. C.	65	♂	12.0	General carcinomatosis	Phthalein, 29 per cent.
109. C. M.	41	♀	12.3	Gastroptosis	
110. G. R.	44	♀	13.5	Hanot's disease	
111. D. T.	37	♀	11.6 12.5	Splanchnoptosis	
112. D.	38	♀	11.1 13.1	Splenomegaly	
113. C.	75	♂	13.5 13.8 12.8	Myositis	Occasional cast
114. F. C.	52	♂	13.0	Adhesions, periduodenal	
115. M. B.	31	♀	14.1	Adhesions, duodenal	Blood pressure, 160/120
116. R. A.	23	♀	14.8	Adhesions, gallbladder, periduodenal	
117. M. G.	36	♀	13.5	Cholecystitis	
118. C. C.	50	♀	14.1	Cholecystitis; chronic pancreatitis	
119. R. S.	32	♀	13.5	Pyelitis, left	Trace of albumin
120. V. O.	44	♂	12.6	Hemiplegia	Trace of albumin
121. S. S.	34	♀	14.1	Enteroptosis; renal calculus	Phthalein, 38 per cent.
122. B. B.	30	♀	12.3	Bronchial asthma	Occasional cast
123. F. P.	43	♂	12.0 10.8 11.1 11.6	Asthma; chronic endocarditis; chronic parenchymatous nephritis	Large amount of albumin; moderate number of casts
124. F. P.	38	♂	13.0 9.8	Incipient interstitial nephritis	Phthalein, 31 per cent.
125. C. B.	56	♂	14.6 12.0	Chronic interstitial nephritis	Blood sugar, 0.222 per cent., 0.183 per cent.; moderate amount of albumin; many casts; phthalein, 22 per cent.; blood pressure, 155/15
126. R. G.	45	♀	13.5 9.9 13.0	Chronic interstitial nephritis; low sugar tolerance	Blood sugar, 0.22 per cent., 0.172 per cent.; 0.177 per cent.; faint trace of albumin, moderate number of casts
127. T. W.	12	♂	14.6	Sydenham's chorea, hypertrophy of tonsils and adenoids	
128. L. G.	41	♀	13.0	Spasmodic stricture of cardiac area of stomach	
129. F. S.	6	♂	13.8	Colitis	
130. A. S.	22	♂	14.8	Flatfoot; partial atrophy of peri-articular surfaces of ankle joints	

breakfast, while the patient is still in a fasting condition, in order to obtain specimens of which the urea values are truer indicators of kidney function than would be the case if the specimens were taken while absorption is in process.

TABLE 4.—Cases with Urea Nitrogen of 15.1 to 18 Mg. Per 100 C.c. of Blood

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
131. J. D.	21	♂	15.8	Perinephritic abscess	Occasional cast
132. M. R.	44	♀	15.8	Chronic appendicitis	
133. R. P.	43	♂	16.5 12.0	Chronic appendicitis; duodenal ulcer	
134. V. D.	35	♂	14.5 17.0	Chronic appendicitis; spastic colitis	
135. J. C.	44	♂	12.0 16.1	Duodenal ulcer	Creatinin, 3.8, 3.4 mg. per 100 c.c.
136. J. C.	31	♂	15.4	Duodenal ulcer; chronic vesiculitis	Moderate number of casts
137. S. P.	39	♂	15.8	Duodenal ulcer	
138. S. K.	52	♂	16.6	Duodenal ulcer	
139. A. K.	31	♂	17.3	Duodenal ulcer; adhesions	
140. M. S.	24	♀	16.1	Gastric ulcer	
141. M. S.	56	♀	15.8	Gastric ulcer	
142. M. L.	48	♂	18.0	Gastric cancer	
143. M. D.	34	♀	16.1	Gastroptosis	
144. T. C.	58	♂	17.0	Chronic gastritis, alcoholic	
145. M. S.	47	♀	15.1	Periduodenal adhesions	
146. W. M.	56	♂	17.6	Periduodenal adhesions	Occasional cast
147. R. Z.	66	♀	16.3	Carcinoma of duodenum	
148. G. B.	47	♂	16.1	General carcinoma of abdomen	
149. B. B.	39	♂	18.0	Partial pyloric obstruction	
150. A. T.	24	♀	15.5	Enteroptosis	Phthalein, 36 per cent.
151. S. G.	23	♂	17.3	Enteroptosis; typhilitis	
152. L. B.	63	♂	17.3	Myocarditis	Trace of albumin
153. A. M.	57	♂	18.0	Myocarditis	Blood pressure, 160/95
154. A. W.	26	♂	17.6	Congenital syphilis	Creatinin, 3.5 mg. per 100 c.c.
155. G. G.	31	♂	15.6	Syphilis; chronic appendicitis	
156. S. K.	69	♂	18.0	Syphilis	Phthalein, 12 per cent.; faint trace of albumin; moderate number of casts
157. A. D.	49	♂	16.2	Syphilis; adhesions; bronchial asthma	Phthalein, 36 per cent.
158. T. D.	46	♂	17.0	Hemiplegia; syphilis	Creatinin, 4.3 mg. per 100 c.c.
159. C. A.	60	♀	16.3	Septic arthritis	Occasional cast; phthalein, 16 per cent.
160. J. G.	52	♂	15.8	Sciatica	Occasional cast
161. H. U.	28	♂	15.8	Hemorrhoids	Phthalein, 20 per cent.
162. J. G.	52	♂	15.5	Typhoid	
163. D. M.	26	♂	16.5	Perineal abscess	Phthalein, 24 per cent., 39 per cent.
164. C. M.	37	♂	15.5	Auricular fibrillation	Moderate number of casts
165. M. S.	12	♂	16.5	Purpura simplex	Blood sugar, 0.168 per cent.
166. W. W.	33	♂	16.1	Amyotrophic lateral sclerosis	
167. E. J.	66	♀	16.1 15.8 13.8	Osler's disease	Trace of albumin; occasional cast
168. T. P.	22	♂	15.5 17.0	Brain tumor	
169. A. M.	46	♂	18.0 15.8	Chronic endocarditis	Occasional cast
170. F. M.	55	♀	16.5	Chronic endocarditis	
171. W. J.	19	♂	15.8	Endocarditis	
172. I. L.	27	♂	16.1	Endocarditis; mitral stenosis	
173. K. R.	67	♀	17.3	Chorea; endocarditis	
174. L. P.	14	♀	17.0	Chorea; endocarditis	
175. I. Z.	37	♂	15.5	Aerophagy	

TABLE 4.—Cases with Urea Nitrogen of 15.1 to 18 Mg. Per 100 C.c. of Blood—(*Continued*)

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
176. S. B.	15	♂	16.1 9.3	Diabetes mellitus	Phthalein, 30 per cent.; blood sugar, 0.336 per cent.; creatinin, 3.6 mg. per 100 c.c.
177. M. J.	57	♂	12.6 16.1	Diabetes mellitus	Blood sugar, 0.300 per cent., 0.188 per cent.; occasional cast
178. A. N.	48	♂	16.1	Acute gangrenous appendicitis	Occasional cast; blood sugar, 0.264 per cent.
179. A. R.	26	♂	15.5	Cecal stasis; chronic appendicitis	
180. S. S.	56	♂	16.5	Hemiparesis; motor aphasia	
181. M. A.	22	♀	18.0 13.8	Cholelithiasis	
182. T. L.	37	♂	16.0	Internal hemorrhoids	
183. F. K.	45	♂	16.0	Cecal stasis	
184. A. B.	22	♀	15.1	Bronchial asthma	
185. H. R.	53	♂	17.5 12.6	Hernia	Faint trace of albumin
186. M. K.	31	♀	16.3 18.0	Lobar pneumonia	Faint trace of albumin
187. L. S.	55	♂	17.8	Arteriosclerosis	Occasional cast; blood pressure, 210/115, 205/160
188. R. S.	57	♀	16.5	Aneurism of aortic arch	Blood sugar, 0.196 per cent.; trace of albumin; occasional cast; blood pressure, 228/112
189. R. S.	50	♂	16.5	Tabes dorsalis	
190. P. F.	48	♂	18.0	Pulmonary tuberculosis	

TABLE 5.—Cases with Urea Nitrogen of 18.1 to 20 Mg. Per 100 C.c. of Blood

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
191. H. B.	36	♂	18.6	General carcinomatosis	
192. N. B.	41	♂	19.0	General carcinomatosis	
193. F. D.	58	♂	19.5	Carcinoma of stomach	Occasional cast
194. E. L.	51	♂	18.6	Duodenal ulcer	
195. F. S.	28	♂	18.3	Duodenal ulcer	
196. T. D.	43	♂	19.0	Gastric or duodenal ulcer	
197. A. A.	39	♂	18.5	Enteroptosis; postpyloric ulcer	Creatinin, 3.6 mg. per 100 c.c.
198. J. M.	43	♂	18.3	Aneurism of aorta	Moderate amount of albumin; casts
199. W. J.	45	♂	19.0	Aortitis; arteriosclerosis	Occasional cast; blood pressure, 205/130
200. M. F.	34	♀	19.0	Hemiplegia	Phthalein, 30 per cent.
201. H. F.	16	♂	18.3	Typhoid	
202. A. B.	62	♀	19.0	Lues; chronic ulcers of leg	
203. J. V.	13	♀	18.3	Chronic parenchymatous nephritis	Trace of albumin; moderate number of casts
204. N. A.	54	♂	19.0 14.7	Chronic endocarditis	Faint trace of albumin; phthalein, 29 per cent.
205. H. O.	60	♀	16.1 19.3	Diabetes	Blood sugar, 0.244 per cent., 0.200 per cent.; occasional cast
206. F. J.	66	♂	18.6	Diabetes mellitus; syphilis; chronic nephritis	Blood sugar, 0.372 per cent.; phthalein, 32 per cent.; trace of albumin; many casts

TABLE 6.—Cases with Urea Nitrogen of 20.1 to 25 Mg. Per 100 C.c. of Blood

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
207. M. K.	47	♂	23.1	Gastric ulcer	Phthalein, 27 per cent.; creatinin, 3.8 mg. per 100 c.c.
208. J. Z.	22	♀	22.5 11.1	Gastric ulcer; marked secondary anemia	
209. A. R.	38	♂	21.1	Duodenal ulcer	Occasional cast; creatinin, 3.5 mg. per 100 c.c.
210. L. W.	41	♂	21.7	Carcinoma of pylorus	Blood sugar, 0.168 per cent.; phthalein, 33 per cent.
211. M. F.	25	♀	23.0	Spastic colitis	
212. M. D.	35	♂	14.5 21.2	Pulmonary tuberculosis	
213. M. A.	44	♂	22.2	Anterior mediosternal tumor	Moderate number of casts
214. S.	58	♂	20.5	Hemorrhagic retinitis	
215. J. P.	56	♂	22.1	Syphilitic aortitis	Phthalein, 28 per cent.
216. J. L.	62	♂	22.2 17.0	Renal hemorrhage; arteriosclerosis; myocarditis	Blood pressure, 195/110, 205/110
217. A. D.	44	♂	20.7 18.6 15.5	Hypopituitarism	Faint trace of albumin; occasional cast
218. M. L.	65	♂	22.7	Myocarditis	
219. J. A.	51	♂	21.8	Myocarditis	Phthalein, 26 per cent.
220. E. H.	56	♀	22.5 14.8	Myocarditis	Trace of albumin; blood pressure, 190/110, 162/102
221. J. C.	47	♂	20.7 12.0	Myocarditis; hypertension; chronic parenchymatous nephritis	Trace of albumin; moderate number of casts
222. J. H.	44	♂	25.0	Chronic myocarditis	Occasional cast
223. L. F.	31	♂	21.1	Interstitial hepatitis; jaundice	Faint trace of albumin; many casts
224. R. B.	60	♂	23.7	Cholelithiasis; renal calculi	
225. S. S.	35	♂	20.8	Chronic endocarditis; mitral regurgitation; mitral stenosis	Blood sugar, 0.168 per cent.; phthalein, 6 per cent., 20 per cent., 22 per cent.
226. F. P.	25	♂	20.7	Chronic prostatitis and vesiculitis	Trace of albumin; occasional cast
227. M. R.	63	♂	21.5 12.0	Chronic interstitial nephritis	Occasional cast
228. M. S.	45	♂	20.5 14.0	Chronic interstitial nephritis	Trace of albumin; many casts
229. A. D.	31	♀	20.5	Duodenal adhesions	

The urea estimations are made by a modified Marshall-Van Slyke method, essentially as described by Myers and Fine.[8] The enzyme used is that derived from the jack bean; the Nessler's solution, made according to the formula of Benedict and Bock, contains 100 gm. of mercuric chlorid, 70 gm. of potassium iodid and 200 gm. of sodium hydroxid per liter of solution.

In our study of this series of analyses we have grouped the cases in six classes on the basis of urea concentration. Cases in which more than one determination was made are listed only in that group in which the highest determination falls. As it seemed desirable to show all evidence of renal impairment, we have also recorded the presence of albumin and casts in the urine, all blood pressures exceeding 150/90,

8. Myers, Fine and Lough: The Archives Int. Med., 1916, **17,** 570.

TABLE 7.—Cases with Urea Nitrogen of 25.1 to 35 Mg. Per 100 C.c. of Blood

Case	Age	Sex	Urea N of Blood, Mg. per 100 C.c.	Diagnosis	Remarks
230. L.	35	♂	29.0 14.5	Spastic paraplegia	Occasional cast; phthalein, 35 per cent.
231. A. M.	48	♂	31.5	Hemiplegia	Occasional cast
232. A. W.	61	♂	34.2	Hemiplegia	
233. P. L.	24	♂	34.2	Bronchitis	Occasional cast
234. I. P.	28	♀	26.0	Chronic constipation	
235. A. M.	29	♂	28.0	Chronic endocarditis; double mitral lesion	Occasional cast; phthalein, 31 per cent.
236. M. K.	8	♂	26.0	Hemorrhagic purpura	
237. J. G.	56	♀	25.5 17.0 21.2	Diabetes mellitus	Trace of albumin
238. I. S.	40	♂	27.7	Diabetes mellitus	Blood sugar, 0.186 per cent.
239. L. H.	56	♀	35.0	Diabetes mellitus Chronic interstitial nephritis	Blood sugar, 0.400 per cent.
240. H. G.	21	♂	23.2 31.5 25.5	Chronic interstitial nephritis	Moderate amount of albumin; occasional cast; creatinin, 3.5, 3.8, 3.2 mg. per 100 c.c.
241. S. G.	50	♂	26.0 28.0 26.0 14.8	Chronic interstitial nephritis and hypertension	Trace of albumin; phthalein, 11 per cent., 23 per cent.; creatinin, 4.2, 5.7, 6.4, 4.6 mg. per 100 c.c.
242. M. M.	51	♀	31.7 35.0 22.2 28.0 16.5 20.0 28.5 33.5	Chronic interstitial nephritis and hypertension	Faint trace of albumin; phthalein, 15 per cent., 9 per cent., 10 per cent., 8 per cent., 8 per cent.; creatinin, 5.5, 5.5, 4.4, 3.3, 3.9, 2.6 mg. per 100 c.c.
243. P. N.	50	♂	27.0 19.5 11.1	Bronchial asthma; chronic parenchymatous nephritis	Moderate amount of albumin; many casts; creatinin, 3.3, 4.6, 2.8 mg. per 100 c.c.
344. W. M.	80	♂	28.0 24.8	Senility	Trace of albumin; moderate number of casts; creatinin, 3.0, 3.8 mg. per 100 c.c.

TABLE 8.—Classification of 206 Cases on the Basis of the Concentration of Urea Nitrogen of the Blood

	Urea N of Blood, Mg. per 100 C.c.	Number of Cases	Percentage of Total Number
Group I	Less than 12.0	31	12.7
Group II	12.0–15.0	99	40.6
Group III	15.1–18.0	60	24.6
Group IV	18.1–20.0	16	6.5
Group V	20.1–25.0	23	9 4
Group VI	25.1–35.0	15	6.1

all phenolsulphonephthalein outputs of less than 40 per cent., all blood sugars of more than 0.16 per cent. and blood creatinins of more than 3.5 mg. per 100 c.c.

These six groups are given in detail in Tables 2 to 7, and are summarized in Tables 8 and 9. From Table 8 it can be readily seen

TABLE 9.—Parallelism of High Concentration of Urea Nitrogen in the Blood and Other Symptoms of Kidney Lesion

	Urea N of Blood, Mg. per 100 C.c.	Number of Cases	Other Symptoms of Kidney Lesions	Percentage
Group I	Less than 12.0	31	11	35
Group II	12.0-15.0	99	38	38
Group III	15.1-18.0	60	26	43
Group IV	18.1-20.0	16	9	56
Group V	20.1-25.0	23	17	74
Group VI	25.1-35.0	15	12	80

that 84 per cent. of the 244 cases examined have a urea nitrogen concentration of not more than 20 mg. per 100 c.c. of blood. Table 9 shows that those groups in which the urea nitrogen of the blood is more than 20 mg. per 100 c.c. contain a greater percentage of cases in which other factors give evidence of kidney lesion than do those groups in which the concentration of urea nitrogen is less than 20 mg. per 100 c.c. Furthermore, the detailed data of Tables 2 to 7 show that in those cases with a urea concentration of less than 20 mg., the other evidence of kidney lesion is generally so slight as to suggest no great loss of functional activity, but in those cases in which the urea concentration is more than 20 mg., the number and character of the other indications of kidney lesion are such as to suggest a more serious impairment of renal function.

On this basis, therefore, it seems reasonable to regard 20 mg. per 100 c.c. as the upper normal limit of urea nitrogen in the blood of hospital patients, and, consequently, to regard all values above 20 mg. as probably pathologic. This conclusion is not very different from that of Folin,[9] who says that among strictly normal persons 14 to 15 mg. is the maximum concentration of urea nitrogen, but that in hospital patients the values are quite as often between 15 and 20 as below 15.

The observations of Squier and Myers[10] regarding the prognostic significance of the blood urea in sixty cases of prostatic obstruction are of interest in this connection. They conclude:

> Cases showing urea nitrogen figures under 20 mg. per 100 c.c. of blood may be regarded as good operative risks, so far as the kidneys are concerned. When the urea nitrogen figures are found between 20 and 30 mg., and especially between 25 and 30, the patient should be operated on with considerable caution, and best after a period of preliminary treatment directed to relieve the nitrogen retention. . . . With urea nitrogen figures over 30, the operative prognosis is bad.

9. Folin, O.: Jour. Am. Med. Assn., 1917, **69,** 1209.
10. Squier, J. B., and Myers, V. C.: Jour. Urol., 1918, **2,** 1.

Study of this series convinces us, moreover, that as a means of estimating renal excretory power the determination of the urea concentration of the blood is, in itself, quite as satisfactory and far more practical than the determination of McLean's index.[11] The difficulty of securing accurately timed specimens of urine from hospital patients needs no emphasis, and inaccurate specimens render the determination of the "index" quite futile. But if the blood urea alone is made the criterion of kidney function, the physician himself can take the specimen and thus eliminate a frequent source of error.

Even were it possible to secure accurate specimens of urine, we would still believe that the determination of the blood urea alone is quite as valuable as the determination of the "index." McLean[11] emphasizes the fact that in nephritis the blood urea frequently lies within normal limits, but the "index" is far below normal. Cases 221, 227 and 228 of this series are of this type. Our records show, however, that the first specimen of blood from these patients always has a moderately high urea nitrogen concentration, and that a diminution of protein in the diet is always followed by a rather slow but very definite diminution of urea nitrogen in the blood. Since this is not characteristic of normal individuals, we believe that successive blood analyses are quite as valuable in the diagnosis of these cases as is the McLean index.

SUMMARY

1. Of 244 hospital patients (medical cases) whose blood had a urea nitrogen concentration of less than 35 mg. per 100 c.c., 206, or 84 per cent., had a concentration of not more than 20 mg. per 100 c.c.

2. Of these 206 cases only eighty-three, or 40 per cent., showed other evidence of renal impairment; but of the remaining thirty-eight cases, twenty-nine, or 77 per cent., showed other renal symptoms.

3. From these observations we conclude that 20 mg. per 100 c.c. may be taken as the upper normal limit of urea nitrogen in the blood of hospital patients, and that for diagnostic purposes the estimation of the blood urea is a satisfactory index of the functioning power of the kidney.

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11. McLean, F. C.: Jour. Am. Med. Assn, 1916, **66**, 415

THE EFFECT OF CONTINUOUS INTRAVENOUS INJECTIONS OF ETHYLHYDROCUPREIN ON EXPERIMENTAL PNEUMOCOCCUS INFECTIONS OF RABBITS*

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The invention of the Woodyatt[1] pump for maintaining intravenous injections over protracted lengths of time has led to the suggestion of several lines of research which are being developed in the Sprague Institute. One of these is presented in this article.

The effectiveness of the in vivo action of a therapeutic agent which is used because of its bactericidal properties, in all probability depends on the same factors which operate in the in vitro action of a bactericide, the two chief of which are the time factor and the concentration factor. Either in vitro or in vivo a given bactericide in a stated length of time will act better on bacteria in a higher concentration than in a lower one, and, in a stated concentration, will act better in a long time than in a short time. (It is important to realize that the latter is not infinitely true, since bacteria which are only inhibited or not entirely killed off by a certain low concentration will in time overcome the inhibition and become acclimated to the bactericide and thereupon grow unrestricted and probably with stimulation.) It is impossible to carry out a complete comparison of the in vitro action with the in vivo action of a chemical, because, in the first place, the concentration within the body is limited by toxicity, and in the second place, the concentration is constantly varying, because of (1) chemical destruction of the chemical or neutralization by oxidation or reduction; (2) chemical combination or conjugation with body constituents, and (3) excretion. The time factor, obviously, varies because of the same reasons.

In our usual methods of administering a drug the curve representing the concentration of the substance in the blood at different intervals will be in the shape of a wave. The steepness of the ascent and descent of the wave will depend on the ratio of the rate of absorption and the size of the dose to the above three factors. The length of time which the drug is effective will depend on the shape of the curve and the concentration at which the drug can be effective.

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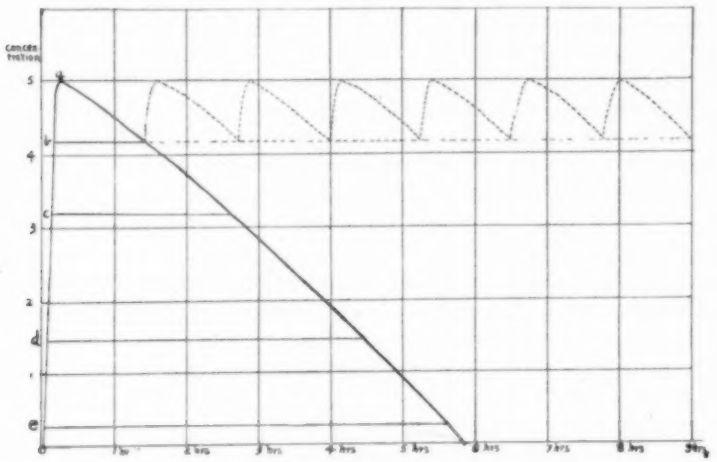
* From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the University of Chicago.

1. Woodyatt: Jour. Biol. Chem., 1917, **39**, 355.

Let the accompanying diagram represent the curve of concentrations which follow the intravenous injection of the largest possible dose of a drug which will not cause toxic symptoms. At once the concentration in the blood rises from zero to the point *a*. Let it be supposed that the three factors mentioned operate so that the concentration decreases at the rate represented by the descending portion of the curve. If the concentration at which the drug is active is at *a*, it is effective only a very short time, but if it is active at *b* it will be effective much longer, and so on, the time of effective action depending on the height of the wave, the rate of its decline, and the concentration of activity. An ideal drug can be pictured in this way showing that such a drug could obtain a high concentration (because of its nontoxicity), would be slow in decreasing this concentration, and would



be highly active at a low concentration. According to the curve, if the drug was active at the concentration *b*, there are two ways in which the time of action could be lengthened: one, by repeating the original dose, or fractions thereof, whenever the concentration fell to *b*. Schematically the concentration in the blood would then be represented by a series of small waves. The second way to maintain an effective concentration would be to introduce the drug *continuously* at a rate which would strike an equilibrium with the rate of operation of the factors which decrease the concentration. In this way the concentration would be schematically represented by a straight line. Such a process as this is now possible since the invention by Woodyatt[1] of a machine which is capable of delivering into the blood stream an accurate amount of fluid at a constant rate.

Let us compare these two suggested methods, first, with the more usual method of medication, and then with each other. While the maintenance of an effective concentration would enhance the action of a drug on bacteria, there would be an increased toxic action on the body tissues. This would, of course, be more marked the nearer the effective concentration approached the toxic concentration. The result would be either a fatal intoxication or a paralysis of the auxiliary forces which operate in the recovery from infections. In the latter case, unless the drug produces a *sterilisans magna*, the unkilled bacteria would be able to grow unrestricted in an almost inert organism. However, if the procedure should kill off all the bacteria, its use would be justified in spite of some toxic action. This is just exactly what does occur in some of our most important forms of medication; for example, in the treatment of syphilis, in which it is the usual procedure to obtain mercurialism and iodism in order to completely kill off the spirochetes. When the concentration is allowed to drop below effectiveness it is possible that in the intervals the bacteria will acquire a "drug resistance" which renders further treatment less effective. On the other hand, in giving frequently repeated doses to maintain an effective concentration, the toxic effect is apt to be more than in the maintenance of a constant concentration which is just effective, because, as represented schematically in the diagram, the concentration occurs in the form of small waves, the crests of which are above the effective concentration but which approach nearer the toxic concentration. In the continuous method a concentration that is above the effective one can be avoided.

It is purposed to follow up this line of research which is opened by the invention of the Woodyatt pump. The plan will be to study the curve of effective concentration in the blood stream, when various drugs are injected intravenously at a continuous and constant rate, on the various physiologic processes, and to put the method to actual test in treating disease conditions.

For various reasons the first drug the study of which has been undertaken in this manner is ethylhydrocuprein (optochin).

After the announcement by Morgenroth and Levy[2] of the discovery and properties of ethylhydrocuprein it was believed that this substance would play an important part in the therapy of pneumococcus infections in man. Quite contrary to these expectations, however, many reports subsequently appeared on the results obtained in its use in these infections, the general trend of which was that in pneumonia the effect of the drug was doubtful, not at all comparable to its in vitro action and to the striking cures obtained by Morgenroth in mice

2. Morganroth and Levy: Berl. klin. Wchnschr., 1911, **48**, 1560 and 1679.

infected with the pneumococcus. In the treatment of exposed pneumococcus infections, as corneal ulcers, where local applications can be made, the drug is of considerable value. As to its value in other local infections, as pleuritis, peritonitis, arthritis, and meningitis caused by the pneumococcus, where direct applications of solutions of ethylhydrocuprein can be made, there seems to be no information.

The studies of Moore[3] present data which give the best information why ethylhydrocuprein is inactive in treating pneumonia. He demonstrated that the drug is slow in action, has small powers of penetration, quickly disappears from the circulation, and has a toxic dose very close to its active dose. For these very reasons, as pointed out in the foregoing, a possible advantage may be found in the continuous injection of the drug. Moore himself anticipated this idea and adopted frequently repeated dosages in his treatments in human infections, but because of the theoretical advantages of the continuous injections over frequently repeated dosage we have not deviated from our purpose, in spite of his negative results.

TECHNIC AND METHODS

Rabbits were chosen as the experimental animal because they are most suitable for the method. In the first place, the easily accessible ear veins make repeated protracted injections possible and easy. Again, the septicemia produced in rabbits by the pneumococcus makes an ideal condition for the in vivo testing of a bactericide. Further, the experimental work that has been done on rabbits with ethylhydrocuprein, in which single dosages were given, has been with negative results.[4] If any beneficial results are obtained they may be justly attributed to the method used.

The descriptions of the Woodyatt pump and its operation have been sufficiently made and a repetition will be omitted here.

The first procedure was to find out the toxicity of ethylhydrocuprein when given inravenously for protracted periods at constant rates. Amounts of the drug were weighed out and dissolved in an amount of 0.9 per cent. sodium chlorid solution, so that when injected at the rate of from 18 to 30 c.c. per hour a certain number of milligrams per kilogram of body weight was delivered. The water used for making the salt solution was redistilled from glass and the sodium chlorid was Merck's fused product. The solution was filtered twice through hard filter paper and sterilized. The syringe of the injecting machine, the buret, rubber tubing and needle were sterilized before

3. Moore and Chesney: THE ARCHIVES INT. MED., 1917, **19,** 611.

4. Scott: Jour. Path. and Bacteriol., 1914-1915, **19,** 130. Boecker: Ztschr. f. Immunitätsforsch. (Orig.), 1915, **24,** 148.

using. As it passed into the vein the fluid was warmed in a bath of warm water. In determining the toxicity, periods of six hours of injection were used and 2, 5, 10, and 15 mg. per kilogram of body weight per hour were given. No symptoms of toxicity were obtained until 15 mg. per kilogram per hour were given. The effect of this amount was inconstant. This amount could be given at times safely for ten hours. At other times death occurred during the first one or two hours of injection. No factor was found which was responsible for this variance. On the other hand, 10 mg. per kilogram per hour could be given indefinitely without apparent toxic symptoms (ten-hour periods on three successive days), although in one instance sudden death occurred during the first hour of a second period of six hours each.

The effect on the bactericidal action of the serum for these rates was studied. Before the injection was started a sample of blood was taken from the heart. After three hours of injection another sample was taken, and another at the end of the injection. The serum from each sample was put in the ice box and next morning they were heated to 56 C. for one-half hour. To equal amounts of each sample 0.5 c.c. of a 1:1,000,000 dilution of a twenty-four-hour broth culture of pneumococcus was added. At various intervals 0.1 c.c. was removed and plated with 10 c.c. of blood agar. At the end of twenty-four hours the colonies on these plates were counted.

There was no effect on the bactericidal action of rabbit serum when ethylhydrocuprein was injected at a rate under 10 mg. per kilogram-hour (Table 1). At this rate, however, there was a slight bactericidal effect, most pronounced at the end of injection. When given at 15 mg. per kilogram-hour there was a rather marked bactericidal effect, most evident, also, at the end of injection (Table 2). This is the first time that it has been shown that ethylhydrocuprein can reach a bactericidal concentration in rabbit's serum, as other workers[5] did not produce it when using single and repeated doses. It has been shown that the failure to obtain such a result with the drug is due to its rapid destruction in the liver (Scott[4]). We surmise that in the continuous injections the power of the liver to destroy or combine ethylhydrocuprein is either fatigued or that the rate of injection exceeds the rate at which the liver can act.

The next procedure was to find the influence of the continuous injection on infections produced in rabbits with the pneumococcus. A twenty-four-hour culture in serum broth of Type 1 was used as the infecting organism. Various intervals of time occurred between experi-

5. Wright: On Pharmacotherapy and Preventive Inoculation Applied to Pneumonia, 1915.

ments and the virulence of the organism varied, but each time the minimum lethal dose[6] (M. L. D.) was determined and the proper controls were made either with the same culture at the time of the ethylhydrocuprein experiment or the day before or after. The infecting dose was given intravenously and was immediately followed by treatment. At the end of each treatment a smear and culture were made from an ear vein, and on death a necropsy was held and cultures made of the heart's blood. The details[7] are given in Table 3.

TABLE 1.—Effect on Bactericidal Action of Rabbit Serum of Giving Ethylhydrocuprein Intravenously at the Rate of 10 Mg. per Kilogram Hour

	After 15 Minutes	After 45 Minutes	After 2 Hours	After 4 Hours	After 7 Hours	After 24 Hours
Normal serum	34	..	46	418		
Three hours of injection	44	18	25	31	24	
Seven hours of injection	37	25	19	44	38	

TABLE 2.—Effect on Bactericidal Action of Rabbit Serum of Giving Ethylhydrocuprein Intravenously at the Rate of 15 Mg. per Kilogram Hour

	Immediately	After 30 Minutes	After 1 Hour	After 2 Hours	After 4 Hours	After 6 Hours	After 24 Hours
Normal serum	15	16	11	18	200	1,000	
Three hours of injection	14	16	18	10	18	46	
Seven hours of injection	19	17	6	6	2	0	0

The results of the experiments can be summarized shortly by saying that in no case was any beneficial effect on the infected animals observed, and in some cases the treated animals died sooner than the controls.

Two modifications of the routine method of treatment were made in an effort to eliminate certain factors which may have been responsible for the negative results. When 21 c.c. are given each hour intravenously, at the end of ten hours there has been injected in all 210 c.c. If no urine, or only a small amount, is excreted in ten hours, the volume

6. A minimum lethal dose is one that will kill within twenty-four hours. If a rabbit overcomes an infection for from thirty-six to forty-eight hours it is not likely to die at all, and in order to be sure of a fatal dose the twenty-four-hour period was selected.

7. At the end of each injection blood cultures were made from an ear vein, and at death smears and cultures were made from the heart's blood; in every case these were positive, and in the last experiment a count of the bacteria showed four times as many in the blood as with the control.

of blood had practically been doubled, which, besides decreasing the concentration of ethylhydrocuprein also decreases the concentration of antibodies. To obviate this the drug was given in a 2 per cent. sodium chlorid solution, which is markedly diuretic. Nevertheless, no improvement in the results was obtained.

Another modification was to give a large initial dose at once and to follow this immediately with periods of continuous injections of 15 mg. per kilogram-hour, of three hours each. The results differed in no way from the others.

TABLE 3.—Results of Treating Rabbits Infected with Pneumococcus with Ethylhydrocuprein Injected Intravenously *

Weight of Rabbit, Gm.	Amount of Optochin per Kilo-Hour, Gm.	Amount of NaCl Solution per Hour, C.c.	Hours of Injection	Dose of Pneumomoccus	Results of Treatment
1,670	0.0082	18	7	1-24 hour slant (5 M. L. D.)	Dead within 2: hours
1,625	0.0074	18	7	1-24 hour slant (5 M. L. D.)	Dead within 24 hours
2,187	0.010	18	First period, 6 hours; second period (after 3¼ hours' interval) 4 hours	2 c.c. of broth culture (5 M. L. D.)	Dead within 24 hours
1,830	0.011	21	First period, 6 hours; next morning, 6 hours	1 c.c. of broth culture (2 M. L. D.)	Died suddenly at the close of second injection
1,680	0.01	21	6	0.5 c.c. of broth culture (5 M. L. D.)	Died within 24 hours
1,700	0.01	21	6 hours after 3 hour interval, 1 hour	0.1 c.c. of broth culture (10 M. L. D.)	Died during injection
1,747	0.01	21	8	0.001 c.c. of broth culture (1 M. L. D.)	Died within 24 hours

* This protocol lists only typical experiments and does not include all experiments done.

While these results do not bear out the theory at the basis of continuous intravenous injections, it is probably because of the nature of the drug and not because of the method. These results lead to the same conclusions as those of Moore, that the drug is useless in the routine treatment of pneumonia.

It is possible that a study of the action of ethylhydrocuprein given continuously in this way on the action of antibodies may explain in some way the paradoxical fact that the pneumococcus septicemia progresses in spite of a demonstrable bactericidal action of the serum.

SUMMARY

1. Ethylhydrocuprein can be given to rabbits intravenously and continuously over protracted lengths of time at the rate of 10 mg. per kilogram per hour, without apparent toxic effects.

2. When injected intravenously into rabbits at the rate of 10 mg. per kilogram per hour for seven hours, ethylhydrocuprein produces

a slight bactericidal action of the serum. A much higher bactericidal action is produced when it is injected at the rate of 15 mg. per kilogram per hour for seven hours.

3. The effect of a fatal dose of pneumococcus on rabbits is not affected by the continuous intravenous injection of ethylhydrocuprein, in spite of the fact that the animal's blood may be distinctly bactericidal in vitro.

4. The continuous intravenous injection of a soluble bactericidal therapeutic drug has theoretical advantages over the usual single or intermittent dosage. The failure of the method with ethylhydrocuprein is probably due to the nature of the drug and not to the method.

AN EXPERIMENTAL STUDY OF SERUM THERAPY IN TRICHINOSIS

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DETROIT

Salzer[1] has published a study of trichinosis in which he claims to have secured beneficial results in man and in experiment animals by the use of serum from patients recovered from the disease. In this connection he also claims that injections of serum are prophylactic against trichinosis; that animals fed with infected meat within twenty-four hours after the administration of the serum might develop a mild form of trichinosis, but if fed at a later period would prove to be immune; and that if immune serum was mixed with infected meat and then fed to animals, the animals did not develop trichinosis, though the ingestion of the same meat without serum was invariably followed by the appearance of the disease. In two patients in the active stages of trichinosis the administration of the serum showed remarkable curative power; there was a decided drop in temperature within six hours and the normal temperature had entirely subsided within twenty-four hours.

Schwartz[2] has categorically taken up Salzer's claims and rejected them, largely on the basis of animal experimentation, in the following language:

> 1. Serum from animals convalescent from trichinosis when injected into other animals did not produce immunity to trichinosis in the latter. 2. Trichinous meat mixed with serum from animals during the active or convalescent stage of the disease proved to be still capable of producing the disease. 3. Animals once infected and harboring trichinae in their muscles were not immune to further infection when fed trichinous meat. 4. Serum from a trichinous animal had no observable ill effects on the larvae freed from their cysts by artificial digestion. 5. None of the results of the experiments appear to be in harmony with the assertions made by Salzer concerning the value of serum from convalescent animals as a prophylactic or curative agent in trichinosis.

We have carried out a nnmber of experiments in testing the prophylactic and curative value of serum from animals recovered from trichinosis, and have come to the following conclusions: So far as our experiments are comparable to those performed by Schwartz, our findings are in agreement with his and tend to disprove Salzer's specific contentions along these lines, but we believe that in spite of

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* Research Laboratory, Parke, Davis and Company.
1. Salzer, B. F.: Jour. Am. Med. Assn., 1916, **67,** 579.
2. Schwartz, Benjamin: Jour. Am. Med. Assn., 1917, **69,** 884.

some erroneous contentions, Salzer may be right in part of his assertions and the treatment he suggests worthy of more approval than Schwartz is inclined to accord to it.

The reason we both agree and disagree with Salzer and with Schwartz is that there are two phases of trichinosis which are not differentiated by either of these writers, though each stands on good ground according to the phase he is considering. Trichinosis is a disease due to the presence in the body of the worm called *Trichinella spiralis* (*Trichina spiralis*). One phase of the disease is a mechanical phase, due to the presence and actions of the worm in the digestive tract, the blood stream, and the musculature. The other phase of the disease is chemical in nature and is due to the presence in the blood of the more or less toxic excretions and secretions of the worm. The first phase of the disease sets up an inflammatory defense reaction which terminates in the walling-in and sealing of the worm cyst in the muscles. The second phase of the disease sets up the customary antibody defense reaction of the blood, which defense reaction becomes manifest in an eosinophilia that may go as high as 86 per cent. and which presumably terminates when the sealing of the worm cyst prevents the excretion and secretion products from reaching the blood stream and when those already present are neutralized or otherwise disposed of and rendered innocuous by the blood.

As regards the first phase, in our opinion, serum has little or no power to prevent the development of the larval worms to adults in the intestines, to prevent the embryo worms from invading the blood stream and tissues, and to prevent these embryo worms from encysting and developing to infective larvae. The experiments performed by Schwartz and ourselves bear out this contention, and so far as Salzer claims the contrary, we believe he is in error.

The claim is occasionally made that worm infestations produce immunity to subsequent infestations with the same worm. For most worms there is a great deal of evidence against the belief and but a small amount in favor of it. It has recently been claimed by Fujinami for schistosomiasis.

As regards the second phase, there seems to be no evident reason why serum from an animal that has recovered from trichinosis should not be of value in protecting another animal from the toxic effects of the secretions and excretions of the worms. These materials, be they specific secretions or waste products of the worm's metabolism, must act like any other foreign protein in the blood in the production of antibodies, and recovery from the disease represents not only the survival of the mechanical damage due to the worm, but an adequate production of antibodies to offset the deleterious effect of these toxic proteins on the body economy. In this connection it might also be

noted that while worm infestations in general are typically afebrile conditions, trichinosis in man is typically febrile, and that the production of the high temperatures has been attributed by some workers to the invasion of the tissues and blood stream by bacteria accompanying the worms. There is exactly the same reason to suppose that the serum of an animal which has recovered from trichinosis would be of value in supplying readymade antibodies to combat toxic worm products, and perhaps accompanying bacterial products, in a case of trichinosis, as there is for believing that serums from immune animals are of value in diphtheria or tetanus. In this respect we are in agreement with Salzer as to the probable value of such a serum, and believe that Schwartz has not attached enough importance to this phase of the subject.

EXPERIMENTS

In undertaking our experiments we first infected a dog in order to obtain a supply of serum. The trichinous pork for feeding to start the experiments was obtained through the kindness of Dr. B. H. Ransom, chief of the Zoological Division of the United States Bureau of Animal Industry, who has made some notable contributions along the line of control of trichinosis through the federal meat inspection service. The infected meat was fed in small lots to two dogs, as follows:

Dog 127.—A mongrel hound weighing 11.5 kg., was given 2 gm. of the meat. Daily examinations of the feces for the next twenty-six days did not show the passage of any trichinae. On the twenty-sixth day the dog was bled from the jugular and then killed with chloroform. Examination of the diaphragm did not disclose any trichinae. The animal may have had a light infection, which was not detected, or it may have been immune to trichinosis, as dogs are commonly resistant to the development of trichinae. Such resistance to infection with species of worms other than those customarily found in a given host species seems to be more a matter of nice adaption to host morphology, temperatures, chemical reaction of the gastro-intestinal secretions, and such inherent physical and chemical conditions, than a matter directly related to any of the blood reactions commonly concerned in immunity.

Dog 129.—A mongrel weighing 15 kg. was given 3 gm. of trichinous meat; twenty-five days later it was fed 2 gm. more; ten days later it was fed 2 gm. more; eleven days later it was fed 4 gm. more; four days later it was fed 4 gm. more; five days later it was fed 5 gm. more; six days later it was fed 5 gm. more; eight days later it was fed 64 gm. more; a total of 89 gm. of trichinous meat. The dog remained active throughout the experiment and did not appear diseased or uncomfortable except for a keratitis beginning the second day after the first feeding and disappearing eighteen days later. The dog was bled from the jugular under chloretone anesthesia 111 days after the first feeding and forty-two days after the last feeding, and the serum separated and preserved with 0.4 per cent. trikresol. The diaphragm was found to be fairly well infested with trichinae.

The animals used for the tests of the serum were white mice. They are easy to infect, but they show little clinical evidence of the disease, so that our tests of efficacy are primarily a consideration of

the longevity of infected rats treated with serum in comparison with check animals similiarly infected but not treated, all animals being kept, so far as possible, under identical conditions of temperature, food, water, etc. The rats were run in series of two to six, one or more serving as checks, and the others receiving various treatments.

We tried guinea-pigs first, feeding them from the same trichinous pork with which the dogs had been fed, but experiments with twelve of them showed that the meat was but slightly infective at this time or the guinea-pigs were resistant, so the diaphragm of Dog 129 was used as the initial infective material and the guinea-pigs dropped in favor of rats. The supply of trichinous meat was kept up by feeding dead experiment rats to new experiment rats. The experiments follow:

Series 1.—To Determine Whether Serum Affects Trichina Larvae

Rat 1 was fed 10 gm. of the diaphragm of Dog 129 and six days later was fed 13 gm. more. Thirty-four days later the rat received a subcutaneous injection of 1 c.c. of the serum from Dog 129. The rat was killed nine days later and the muscles found infested. It was used to infest other rats.

Rat 2 was fed the same amounts at the same time as Rat 1. It was injected the same day, but received 2 c.c. of serum. It died forty-four days after the injection, and the muscles were found infested and infective for other rats.

This experiment only indicates that serum exerts no evident bad effect on trichinae when used at the interval and in the amount given, the trichinae being alive and infective for susceptible animals.

Series 2.—To Determine the Effect of Simultaneous Injection and Feeding

Rat 1 was fed 1 gm. of meat from Rat 1 of Series I, and was injected at the same time with 1 c.c. of serum. The rat escaped while a temperature was being taken and was soaked with cold water before it was captured. It was found dead the next day. Postmortem examination showed pneumonia. This animal cannot be considered in determining the results of the experiments.

Rat 2 was fed 1 gm. of meat from Rat 1 of Series 1, and was injected at about the same time with 2 c.c. of serum. The following day it was fed 1 gm. more of the meat. Two days after this second feeding the rat was almost dead, so it was killed. The intestine was hemorrhagic and scrapings showed numerous trichinae.

Rat 3, the check, was fed the same amounts and at the same time as Rat 2, but was given no serum. This rat died either the afternoon of the day it was fed the second time or the following day. The intestine was hemorrhagic and showed numerous trichinae, especially in the duodenum.

In this experiment the treated animal outlived the check a short time, one or two days.

Series 3.—To Test the Prophylactic Value of Serum Simultaneously Injected or on Food

Rat 1 was fed 2 gm. of trichinous meat and was injected at the same time with 1.5 c.c. of serum. Eight days later it was fed 1 gm. more. Forty days after the second feeding it was fed 1 gm. more. Six days after this last feeding the rat was killed. The muscles were heavily infested.

Rat 2 was fed the same amounts and at the same time as Rat 1, but the first feed of trichinous meat was mixed with 5 c.c. of serum before feeding. In addition to the feedings at the same time as Rat 1, this rat was fed 1 gm. of meat the day Rat 1 was killed. Four days later it was fed 1 gm. more; six days after this feeding it was fed 1 gm. more. Five days after the last

feeding it was found dead. The intestine was hemorrhagic and contained trichinae. Trichinae were abundant in the muscles.

Rat 3, a check, was fed the first two times that the others were fed, getting the same amount of trichinous meat. Two days after the second feeding the rat was found dead. No trichinae were found in the diaphragm or intestines.

In this experiment the rats receiving the serum outlived the check rat decidedly, but it was impossible to associate definitely the death of the check animal with the feeding of trichina. Experiments show, however, that neither the injection nor the feeding of serum prevented infection with trichinae.

Series 4.—To Test the Prophylactic Value of Serum Simultaneously Injected or on Food

Rat 1 was fed 1 gm. of meat mixed with 1 c.c. of serum. Additional feedings of 1 gm. each were made on the third, tenth, fourteenth and twentieth days after the first feeding, but no serum was given with these feedings. The day after the last feeding the rat was found dead. The intestines were hemorrhagic and the lungs pneumonic. Trichinae were found in the intestines and musculature.

Rat 2 was fed the same amounts and at the same time as Rat 1, but the first gram of meat was mixed with 2 c.c. of serum. Following the death of the first rat, No. 2 was fed additional meat as follows: 24 days after the first feeding, 0.5 gm.; 28 days, 1 gm.; 38 days, 1 gm.; 45 days, 2 gm.; 52 days, 1 gm.; 57 days, 1 gm.; 63 days, 1 gm.; 68 days, 0.5 gm. The rat died the day after the last feeding. The lung was pneumonic and presented tubercles, the nature of which was not determined. There were trichinae in the intestine and the musculature showed a very heavy infestation. Trichinae were present in the scalp muscles, the eye muscles and in some coats of the eye.

Rat 3 was fed the same amounts and at the same time as Rat 1, but received an injection of 1 c.c. of serum when the first gram of meat was fed. This rat died five days after Rat 1. The stomach and small intestine were hemorrhagic and the lungs pneumonic. There were trichinae in the intestine and musculature.

Rat 4 was fed the same amounts and at the same time as Rat 2, but received an injection of 2 c.c. of serum at the time the first gram of meat was fed. This rat also received an additional 0.5 gm. of meat seven days after the last feeding of Rat 2. Ten days after this feeding the rat was found dead. This rat showed a pronounced edema of the eyelids and the left eye became purulent and blind. Trichinae were found in the intestine and the muscles were heavily infested.

Rat 5, a check, was fed the same amounts and at the same time as Rat 1, but received no serum. In addition it was fed 0.5 gm. of meat four days after the last feeding of Rat 1, and 1 gm. eight days after the last feeding of Rat 1. Two days later the rat began to develop nervous symptoms. It would fall to the right side and could hardly assume or maintain an erect position. Four days later the condition was more marked and the rat would roll over and over to the right unless restrained by some limiting object on that side. Eight days after its last feeding the rat was found dead. The intestine was hemorrhagic and the lungs pneumonic. Trichinae were found in the intestine and in the diaphragm.

Rat 6, a check, was fed the same amounts and at the same time as Rat 5. In addition it was fed 1 gm. of meat ten days after the last feeding of Rat 5 and 2 gm. seventeen days after the last feeding of Rat 5. Eight days after its last feeding the rat was found dead. There was a severe hemorrhagic condition in the jejunum, less severe in the duodenum, and the lungs were pneumonic. Trichinae were found in the intestine and diaphragm.

It will be seen from the foregoing that the serum, injected or fed with the trichinous meat had no evident prophylactic value.

As regards the curative value of the serum, as judged by comparative longevity of the treated animals and the checks, we find the following:

Two of the treated animals, those receiving the largest amounts of serum by injection or feeding, outlived both the checks, and both the checks outlived the other two treated animals, those receiving the smallest amount of serum by injection or feeding. As the feedings were kept up, the survivors in all cases received larger amounts of meat than the animals outlived by them. The animals receiving the larger amount of serum outlived the checks by totals of 120 days, while the checks outlived the animals receiving the smaller amount of serum by totals of eighty-four days. This leaves a slight presumption in favor of the idea that there is some value in the treatment. The severity of infestation in Rats 2 and 4 may be fairly associated with their additional feedings.

Series 5.—To Test the Prophylactic Value of Simultaneous and 3 and 4 C.c. Injections of Serum

Rat 1 was fed 2 gm. of meat and at the same time was given a subcutaneous injection of 3 c.c. of serum. Seven days later it was fed 2 gm. more of meat; seventeen days later, 2 gm. more; twenty-four days later, 1 gm. more, and twenty-nine days after the first feeding was fed 1 gm. more. Two days later the rat was found dead. The lungs showed hepatized areas, the liver was light colored and apparently degenerated. Trichinae were found in the intestine, and the diaphragm was rather lightly infested.

Rat 2 was given two feedings at the same time that Rat 1 received its first two, and got the same amounts, but was given an injection of 4 c.c. of serum at the time of the first feeding. Seventeen days after the first feeding it was found dead. The lungs showed areas of hepatization and there was some blood in the intestine. Trichinae were plentiful in the intestine, but the diaphragm was very lightly infested.

Rat 3, a check, was fed four times at the time Rat 1 received its first four feedings, and received the same amounts as Rat 1. Five days after the last feeding this rat was found dead. The lungs were pneumonic and the jejunum hemorrhagic. There were trichinae in the intestine and the diaphragm was very heavily infested.

While the injections of large amounts of serum, 3 or 4 c.c., did not prevent infestation with trichinae in Rats 1 and 2, it is nevertheless interesting to note that these rats, which had been fed five times and two times, had very light infestation with trichinae, while the check rat, which was fed four times, had a very heavy infestation.

As regards longevity, a treated rat outlived the check nine days and the check outlived the other treated rat five days, a margin in favor of the treated animals.

Series 6.—To Test the Prophylactic Value of Injections Previous to Feeding

Rat 1 was injected with 1 c.c. of serum and fed 1 gm. of heavily infested meat the next day. One week after each of these proceedings, the injection and the feeding were repeated. Five days after the second injection of serum it was repeated, followed by the feeding of a gram of the meat the next day, making a total of three injections of 1 c.c. of serum followed each time by feeding 1 gm. of meat the next day. Four days after the last feeding the rat was found dead. The lungs were pneumonic. A moderate number of trichinae were found in the intestine, but none in the diaphragm at that date.

Rat 2 received the same treatment, as regards serum and trichinous meat, that Rat 1 received. This animal lived and enjoyed good health for fifty-eight days and was killed at that time to permit of postmortem observations and to close up the experiment. The anterior portion of the right lung presented tubercles and was adherent to the chest wall at this point. There were no

trichinae found in the intestine and only a very moderate number in the diaphragm.

Rat 3, a check, was fed the same amount of trichinous meat at the same time as the other rats, but was given no serum. This rat died five days after the last feeding. The intestine was hemorrhagic and heavily infested with trichinae. No trichinae were found in the diaphragm at this time.

As regards longevity, the check outlived one treated animal by one day, but the other treated animal outlived the check by thirty-nine days and was killed when it had evidently outlived any danger from its trichina feeding and apparently would have lived much longer.

As regards development of trichina, the check rat had a much larger number in the intestine than the treated Rat 1; these two rats did not show somatic trichinosis, but died too soon to permit of conclusions in regard to this. Rat 3 lived long enough to lose its intestinal trichinosis and had acquired a mild somatic infestation.

SUMMARY OF EXPERIMENTAL DATA

A summary of the foregoing data on longevity shows: Of fifteen rats, those given the serum treatment outlived the checks in nine cases, whereas the checks outlived those given the serum in six cases. In two cases the treated animals were killed instead of being allowed to die. The figures for each series are as follows:

Series 2: Treated animal outlived the check by one or two days.

Series 3: Treated animals lived an average of 62.5 days; the check, 11 days. Treated animals lived on an average 51.5 days longer than the check.

Series 4: Treated animals lived an average of 51.25 days; checks, 45.5 days. Treated animals lived on an average 5.75 days longer than the checks.

Series 5: Treated animals lived an average of 25 days; the check, 23 days. Treated animals lived on an average 2 days longer than the check.

Series 6: Treated animals lived on an average 37 (plus) days; the check, 18 days. Treated animals lived on an average 19 (plus) days longer than the check.

Note that treated animals outlived the checks in every series, the total number of days which treated animals survived the checks being 80 (plus).

From what we know of antibody production it appears, then, entirely likely that serum from an animal recovered from trichinosis would be of value in combating the toxic features of the disease. Our experiments seem to bear out this idea. The experiments are by no means proof of the value of the treatment, but they are evidence which accords with the theoretic possibilities and with Salzer's good clinical results in two of his cases, which results deserve to be considered apart from what appear to be undemonstrable claims in regard to serum inhibition of trichina development.

The clinical picture of trichinosis in rats is not a well defined affair as in man. Rats are the habitual and normal hosts of trichinae and probably have an inherent tolerance for these worms. Raebiger[3] found no eosinophilis in the blood of trichinous rats and but few eosinophils around the encysted trichinae, though Opie[4] found eosinophilia beginning at the end of the second week. Rats show little evidence of myalgia and the pyrexia present in man seems to be lacking. The day after rats are fed trichinae there is usually a marked fall of temperature, followed by a rise to normal the following day, or a slow rise for several days. Such data as we have on this point (temperatures were not taken on Sundays) shows that twenty-four hours after feeding trichinous meat without serum in any form, the temperature dropped 42 times, an average drop of 1.9 degrees, and rose 19 times, an average rise of 1.1 degrees. Where trichinous meat was fed and serum injected at the same time the temperature dropped 5 times, an average of 0.96 degree, and rose once, 1 degree. Where trichinous meat was fed after being mixed with serum the temperature dropped in both of two cases, 0.3 and 1.2 degrees. Where serum was injected without trichinous meat being fed the same day the temperature dropped 4 times, an average of 0.56 degree, and rose 4 times, an average of 0.7 degree. The greatest fall of temperature followed by recovery was in the case of Rat 1 of Series 4; on the third feeding the temperature dropped from 99.8 F. the day of feeding to 95.5 the following day, a drop of 4.3 degrees, but rose to 99 the next day. The greatest rise in temperature was in the case of Rat 4 of Series 4; on the sixth feeding the temperature rose from 97.6 to 101, a rise of 3.4 degrees.

The usual fall in temperature seems to be associated with a marked enteritis. There is usually blood in the feces and rectum the day after feeding trichinous meat, a condition that may visibly persist for as many as four days after feeding. Associated with this is a diarrhea and more or less gas in the intestine. Pneumonic conditions were rather common in these rats, perhaps due to the passage of embryos through the pulmonary capillaries. The edema of the eyelids, which is comparatively common in trichinosis in man, was only detected once in our rats.

The fact that rats are extremely tolerant of trichinae and do not present a clinical picture comparable to that in man, and the fact that other experiment animals are open to the same objection (experimental feeding to a shoat failed to develop pyrexia, though 83 gm. of trichinous meat were fed in thirty-three days) or are open to the objection

3. Raebiger, S.: Ztschr. f. Infektionskr. d. Haustiere, 1911, **9**, 120.
4. Opie, E. L.: Am. Jour. Med. Sc., 1908, **127**, 477.

that they are difficult to infect, suggests that the value of immune serum in trichinosis can hardly be ascertained except by clinical test on human patients. The lack of febrile conditions in rats, or in the shoat just mentioned, suggests that in these animals there is an inherent immunity to the second phase of trichinosis, the phase associated with toxic products in the blood and with antibody production against the toxins. Rats and swine have presumably acquired this immunity through ages of infestation and apparently suffer primarily from the first phase of the disease, the mechanical phase, against which no immunity could readily be developed. Man, in a comparatively short and limited experience in feeding on raw trichinous pork, has developed no such immunity to the second phase of trichinosis.

In view of the fact that our present day treatment of trichinosis is mostly palliative and symptomatic, a serum treatment might be of considerable therapeutic value. Its commercial value would be slight. The number of cases of trichinosis in the United States yearly is not large; the serum from one horse which had been properly immunized by feedings of trichinae would probably more than supply treatment for all cases. Such production could only be profitably undertaken by a firm selling directly from a central plant; it could not be profitably undertaken by a firm with numerous branch houses to be restocked yearly.

SUMMARY AND CONCLUSIONS

Our experiments bear out the conclusions of Schwartz to the effect that serum from animals convalescent from trichinosis, when injected into other animals or fed to them mixed with trichinous meat, does not inhibit the customary development of trichinae.

On the other hand, theoretic considerations, the clinical observations of Salzer, and the longevity data from our expriments lead us to the conclusion that such a serum may be of decided value in combating the toxic features of trichinosis, a conclusion which is in general agreement with Salzer's belief in the value of such a serum.

METABOLISM IN A CASE OF HEMOCHROMATOSIS*

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Meltzer,[1] in 1900, and Parker,[2] in 1903, suggested that the deposition of iron-containing pigment in the tissues in hemochromatosis was in part the result of faulty retention of iron. This view was given support in a more recent article edited by Garrod[3] in which Mackenzie Wallis stated that no iron was found in the feces, urine, or bile of a case of hemochromatosis while a slight increase in the iron content of the blood was present. Mackenzie Wallis was unable to carry out metabolism studies in his case, but he emphasized the importance of such work. Howard and Stevens[4] have recently reported the first accurate metabolism studies in this disease. Their publication gives an excellent discussion of what is known concerning its chemistry. In the report here presented additional metabolism studies on a case of hemochromatosis have been made.

METHODS

The patient was given the following diet:

FOOD MIXTURE

Milk	625 c.c.
Cream (40%)	275 c.c.
Eggs	550 gm.
Malted milk	60 gm.
Water up to	2,500 c.c.

This diet did not exceed the carbohydrate tolerance of the patient as judged by the absence of sugar from the urine throughout the period of the metabolism experiment. Feedings were given at two hourly intervals from 7 a. m. to 7 p. m. With each of the first morning feedings the patient was given a gelatin capsule containing from 0.187 to 0.210 gm. of ferric ammonium citrate. The stools at the beginning and the end of the experiment were demarcated by adding 2 gm. of charcoal to the first and last feedings. The patient was given the diet one day prior to beginning the collection of specimens. The metabolism experiment was of five days' duration. All the stools were collected in porcelain containers, mixed with 2 per cent. hydrochloric acid in

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* From the medical clinic of the Peter Bent Brigham Hospital.

1. Meltzer, S. J.: The Pathogenesis of General Hemochromatosis (Diabète bronzé). Med. Rec., New York, 1900, **57,** 43.

2. Parker: Case of Bronze Diabetes. Brit. Med. Jour., 1903, **2,** 1052.

3. Gaskell, J. F., Sladden, A. E., Mackenzie, Wallace R. L., Vaile, P. T., Garrod, A. E.: A Contribution to the Study of Bronze Diabetes. Quart. Jour. Med., 1913-1914, **7,** 129.

4. Howard, C. P., and Stevens, F. A.: The Iron Metabolism of Hemochromatosis. THE ARCHIVES INT. MED., 1917, **20,** 896.

95 per cent. alcohol and dried to constant weight at 50 C. Aliquot portions of each day's food were mixed and kept under toluol on ice. The urine was preserved under toluol on ice.

Nitrogen was determined by the Kjeldahl method and ammonia by the aeration method of Folin.[5] Iron was determined by the method of Neumann.[6] The total sulphur was quantitated by Benedict's[7] method. The food and feces were prepared for the sulphur determination in the way outlined by Baumann and Howard.[8] To determine phosphorus the food, feces or urine were first ashed by Neumann's method. The phosphorus was precipitated as ammonium phosphomolybdate and determined volumetrically. Calcium and magnesium were quantitated by McCrudden's method.[9] The food and feces were prepared, in the analysis for calcium and magnesium, by the procedure outlined by Baumann and Howard. Potassium and sodium were determined in the solution obtained by ashing according to Neumann's method. They were obtained as the chlorids and then the potassium as the chloroplatinate by the usual methods. In determining chlorin, sodium carbonate (Na_2CO_3) was added to the urine or food and the whole evaporated to dryness in a platinum dish on the water-bath. The residue was incinerated, avoiding red heat. The ash was extracted with cold nitric acid (HNO_3), the residue heated until white, the acid extract added and the whole evaporated to dryness. The residue was extracted with dilute nitric acid and the chlorin titrated according to Mohr's method.[10] Urea was determined by the method of Van Slyke and Cullen,[11] and total nonprotein nitrogen in the blood by that of Folin.[12] Blood fats were estimated by Bloor's method.[13] The basal metabolism was determined by the method of indirect calorimetry. The usual mask covering the nose and mouth was used. The expired air was collected in a Tissot spirometer. Analyses for oxygen (O_2) and carbon dioxid (CO_2) were made with the Haldane gas analysis apparatus. The patient was kept at complete rest in bed without food or drink for eight hours prior to running the basal metabolism experiment.

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8. Baumann, L., Howard, C. P.: Metabolism of Scurvy in an Adult. The Archives Int. Med., 1912, **9,** 665.

9. McCrudden, F.: The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron Devised Especially for the Analysis of Foods, Urine and Feces, Biol. Chem., 1910, **7,** 83. The Determination of Calcium in the Presence of Magnesium and Phosphates: the Determination of Calcium in Urine, Jour. Biol. Chem., 1911, **10,** 187.

10. Hawk, P. B.: Practical Physiol. Chem., Philadelphia, 1916.

11. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in Determination of Urea, Jour. Biol. Chem., 1914, **19,** 211.

12. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. II. Nonprotein Nitrogen in Blood, Jour. Biol. Chem., 1916, **26,** 491.

13. Bloor, W. R.: Nephelometric Method for the Determination of Fat in Blood, Jour. Biol. Chem., 1911, **17,** 377. A Method for the Determination of "Lecithin" in Small Amounts of Blood, Jour. Biol. Chem., 1915, **22,** 133. The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, Jour. Biol. Chem., 1916, **27,** 107.

SYNOPSIS OF THE CASE REPORT

History.—W. W. S., Med. No. 6565, white man, aged 52, was admitted to the Peter Bent Brigham Hospital, May 7, 1917, and discharged improved June 3, 1917. Complaint, "weakness and sciatica." The family and marital history are unimportant. Habits: The patient did not use alcoholic drinks. He used tobacco in moderation, but took no drugs. Occupation: Police officer. He stopped work April 8, 1917, because of present illness.

Past Medical History.—The patient was born in Scotland and had lived in America forty-five years. He had scarlet fever as a baby, influenza nineteen years and typhoid fever nine years prior to admission. He had had a broken arm and four broken ribs. A hydrocele was tapped in October, 1916. The past medical history was otherwise negative.

Weight: Patient weighed 215 pounds five years prior to admission. His present weight was 180, 25 pounds having been lost since January, 1917.

Present Illness.—For several years the patient had had occasional attacks of sciatica-like pains in the right thigh. Since January, 1917, this symptom had grown worse and was constantly present on admission to the hospital. Since that time he had become progressively weaker physically. For the last few weeks there had been a sensation of numbness beginning in the lips and radiating down the left arm. Polydypsia, polyphagia or polyuria were not present.

Physical Examination.—The patient was a well developed, fairly well nourished although somewhat gaunt looking man. The skin of the neck, face, forearms and legs was diffusely pigmented and dark brown in color. The skin of the remainder of the body was also pigmented but to a less degree. Liver dulness began at the fifth rib anteriorly. The edge of the liver was palpable 5 cm. below the costal margin in the right mammary line. It was smooth and nontender. The spleen was palpable 2 cm. below the left costal margin. The edge was sharp, firm and nontender. Examination of the heart gave no abnormal findings. Blood pressure was 115 mm. systolic and 65 mm. diastolic. There was some stiffness and pain in the right knee on motion. A roentgenogram of the joint showed hypertrophic bony changes. The remainder of the physical examination was negative.

Laboratory Findings.—May 7. Blood examination: Hemoglobin was 75 per cent. (Sahli). White cells were 5,600 per c.mm. The differential count was 50 per cent. polymorphonuclears, 45 per cent. lymphocytes, 5 per cent. large mononuclears. May 31: Hemoglobin was 88 per cent.; red cells were 5,680,000 per c.mm., and white cells 5,400 per c.mm. May 8: Urine examination, 2,100 c.c., amber; acid; specific gravity 1.025; no albumin; 15 gm. (1.5 per cent.) glucose; no acetone; no bile; no erythrocytes; no leukocytes; a few hyaline casts. Examination of the feces for blood and other pathologic elements was negative. The Wassermann reaction in the blood serum was negative. The cerebrospinal fluid contained 4 cells per c.mm. but no globulin by the Nonne test, and the Wassermann reaction was negative in 1 c.c. May 23, the McLean index of urea excretion was 143 per cent. There were 8.6 mg. of urea nitrogen per 100 c.c. of blood. May 15 the carbon dioxid tension in the alveolar air was 36 mm. of mercury. Dr. F. B. Mallory of the Boston City Hospital made the following report on the histologic examination of a piece of skin removed from the patient's arm:

The section of skin shows two types of pigment. In the lower layers of the epithelium, mainly in the basement cells, there is a fairly fine pigment of yellowish brown color, diffusely scattered through the cells. In the corium there is another pigment of a brownish yellow color which gives the typical iron reaction with the Nishimura stain for hemosiderin. This pigment is fairly abundant, especially around the coil glands and the blood vessels. It seems to be, certainly for the most part, within the cytoplasm of the connective tissue cells. Insofar as this particular tissue goes, it is indicative of a pigmentation due to an iron-containing pigment and in its distribution is

similar to what we have seen in other cases which have come to necropsy, and has all the lesions of hemochromatosis in its typical form.

Progress of the Case.—The patient's urine became free from sugar by limiting the diet to 30 gm. of carbohydrate and 15 gm. of protein. By May 22 he was able to take a diet containing 75 gm. of carbohydrate, 75 gm. of protein and 175 gm. of fat without sugar appearing in the urine. The symptoms of sciatic neuritis disappeared. Pain developed in the upper left chest. The roentgen-ray examination showed a separation of the cartilage and bone of the first left rib, but no other pathology. Relief from this pain was not obtained until a week after the patient left the hospital. The patient's temperature varied from 98 to 99 F. On the evening of May 29 and the morning of the 30th the temperature reached 100 but by evening had fallen to 98.6. The quantity of urine usually varied from 600 c.c. to 1,600 c.c. in the twenty-four hours. May 7 it was 2,100 c.c. and on the 23d it was 2,600 c.c.

EXPERIMENTAL FINDINGS

Analyses of the various substances made in the food, urine, feces and blood in the iron metabolism experiment are given in Table 1. During the experiment the patient ingested 10,242 c.c. of the food mixture and 0.9858 gm. of ferric ammonium citrate. He excreted 4,260 c.c. of urine. The weight of the dried stools for the entire period was 161.8 gm.

The balance of nitrogen and inorganic constituents, except iron, was negative (Table 1). The patient ingested 240 mg. of iron and excreted 0.192 mg. in the feces. None was eliminated in the urine. The total amount of fat, the fat partition and the amounts of creatin,[14] of creatinin,[14] of urea nitrogen and of nonprotein nitrogen in the blood were normal. The significance of these findings will be discussed later.

The basal heat production, as determined by the method of indirect calorimetry, was obtained with the assistance of Dr. J. A. Wentworth. The experimental findings are given in Table 2.

A study of Table 2 shows that both the respiratory quotient and the heat production were normal. These findings demonstrate that there was no gross disturbance in the patient's intermediary metabolism.

SUMMARY AND DISCUSSION

Twenty per cent. (0.048) of the iron ingested by the patient was not recovered in the feces. None was present in the urine. In the case reported by Howard and Stevens 8.5 per cent. (0.0025 gm.) of the iron fed was not regained. Any one explanation for the failure to completely recover the iron administered during these experiments is open to criticism. This is due to the fact that not enough is known regarding the metabolism of iron in the normal person to permit unquestionable deductions to be drawn from the findings in pathologic conditions. It is natural to expect that a certain amount of any sub-

14. Determinations made by Dr. E. A. Doisy.

TABLE 1.—Metabolism Experiment, May 25 to 30, 1917, on a Case of Hemochromatosis *

Substance Analyzed	Nitrogen in Gm.	NH_3 in Gm.	S in Gm.	P in Gm.	Ca in Gm.	Mg in Gm.	Na in Gm.	K in Gm	Fe in Gm.	Cl in Gm.	Fatty Acids in Mg. per 100 C.c.	Cholesterol in Mg. per 100 C.c.	Lecithin in Mg. per 100 C.c.	Urea Nitrogen in Mg. per 100 C.c.	Non-protein Nitrogen in Mg. per 100 C.c.
Whole blood	.....	.....	.....	.....	.....	.....	.....	.....	0.048†	.....	400‡	200‡	270‡	11.0	30.0
Blood plasma	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	370‡	230‡	185‡		
Food	66.47	.....	4.503	6.810	5.762	0.807	15.754	7.807	0.240	28.267					
Urine	59.09	6.30	4.835	6.561	3.734	0.597	15.172	6.505	0	16.358					
Feces	8.85	.....	0.769	1.165	2.742	0.539	2.097	3.579	0.192						
Balance	—1.38	.....	—1.100	—0.917	—0.715	—0.269	—1.516	—2.277	+0.048						

* Weight of patient 75 kilograms. † Milligrams per 100 c.c. of blood. ‡ Analysis by Dr. W. R. Bloor.

TABLE 2.—Basal Metabolism, May 11, 1917, in Hemochromatosis

Patient's height, 178 cm.; weight, 77.8 kg.; surface area, 1.96 sq. m.; temperature (r), 98.4 F.

Period	Percentage CO_2 Production	Percentage O_2 Consumption	CO_2 Production per Minute in C.c.	O_2 Consumption per Minute in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent. Below or Above Average Basal Linear Metabolism	Minute Volume in Liters	Rate of Respiration per Minute	Volume of Respiration per Minute in C.c.	Pulse Rate per Minute	Time of Experimental Period in Minutes
I	3.06	4.21	190	262	0.73	37.8	+0.9	6.23	17.7	352	59	9.98
II	3.06	4.14	183	246	0.74	35.7	—4.9	5.95	16.7	356	61	9.97
Average	3.07	4.18	187	254	0.74	36.8	—2.0	6.09	17.2	354	60	

stance may be lost in its passage through the body. This explanation could account for the small amount of iron not recovered in the case reported by Howard and Stevens. Gottlieb[15] has shown that in dogs, subcutaneously injected iron may require a period of many days for its complete excretion. The collection of the stools for analysis in the case here reported was limited to those feces derived from the iron-containing food fed. For this reason the failure to recover all of the iron administered to this patient may have been due to a lag in its excretion. The careful studies of Queckenstedt[16] have shown that all the iron administered to patients in whom there was no reason to suspect causes for the abnormal retention of that substance was not completely excreted during the period of the experiments. This observer reported the retention of considerable amounts of iron in two cases of chronic endocarditis and three cases of pernicious anemia. In these cases from 35 per cent. to 51 per cent. and from 8 to 35 mg. of the iron fed were not again recovered during the periods of the experiments. From this discussion it is evident that the failure to recover all of the iron administered during the experiment here recorded, and in the one reported by Howard and Stevens, does not prove that there is an abnormal retention of iron in the disease, hemochromatosis. Nevertheless, it tends to support the hypothesis based on the assumption that such an abnormal retention does occur. If the latter is true, the experimental findings do not in any way show whether the fault lies in a disturbed metabolism, or in the excretory function of iron. The latter view was held by Garrod. He considered that the power of the body to excrete iron was markedly diminished. The view of Garrod is rendered untenable by the findings that the greater part of the ingested iron is eliminated in this disease.

The finding of 0.048 gm. of iron per 100 c.c. of blood cannot be considered an abnormally large amount of that substance in the blood. Although Garrod states that 0.042 gm. of iron is the maximum normal amount, Howard and Stevens show this to be erroneous.

The amount of protein in the food ingested during the metabolism experiment (Table 1) represented the minimum theoretical requirement for a normal man at rest in bed and of a body weight of 75 kg. The quantities of inorganic food elements, with the exception of iron, were somewhat less than are usually fed (Footnotes 8 and 17). The

15. Gottlieb, R.: Ueber die Ausscheidungsverhältnissen des Eisens, Ztschr. f. physiol. Chem., 1891, **15,** 371.

16. Queckenstedt: Untersuchungen über den Eisenstoffwechsel bei der perniözen Anämie, mit Bemerkungen über den Eisentoffwechsel uberhaupt, Ztschr. f. klin. Med., 1913-1914, **79,** 49.

17. Folin, O.: Approximately Complete Analyses of Thirty "Normal" Urines, Am. Jour. Physiol., 1905, **13,** 45.

comparatively low values for the different constituents of the food ingested during the experiment probably explain the small losses of nitrogen and the inorganic substances which occurred (Table 1). If this explanation is correct, then the finding of the negative balances of the different substances studied in this experiment show that there was no disturbance in the metabolism as a result of the diseased condition, hemochromatosis. This result corroborates the findings of Howard and Stevens.

The studies made have failed to prove the existence of disturbances in the metabolism of the case here reported. Nevertheless, from the clinical and pathologic knowledge concerning hemochromatosis it is very probable that the disease is an expression of some derangement in metabolism.

CONCLUSIONS

1. A retention of food iron has been found in a metabolism experiment on a case of hemochromatosis. Whether or not this retention is to be considered as abnormal is unknown. Nevertheless, the hypothesis that there is an abnormal retention of iron in hemochromatosis is consistent with the experimental findings.

2. The basal metabolism and the respiratory quotient, determined by indirect calorimetry, were normal. These findings show that there was no gross disturbance in the intermediary metabolism.

I wish to thank Dr. F. W. Peabody for permission to carry out the respiratory metabolism experiments in his laboratory at the Peter Bent Brigham Hospital. Mr. A. S. Wetmore made most of the determinations of the inorganic elements. Certain of the analyses were made in the chemical laboratory of St. Luke's Hospital, Bethlehem, Pa.

EXPERIMENTAL BACTEREMIA*

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A study of the effect of organisms on rabbits' appendixes when intravenously injected showed that this organ in these animals was not always the tissue most seriously attacked, and, furthermore, was never the only organ to exhibit alterations in its structure. The injection of large doses of active cultures produced a widely disseminated infection, with the development of lesions in several different organs. Although the material was selected with a view to demonstrate an elective affinity on the part of the organisms for the appendix, we were unable to determine such an affinity, even though the appendix was affected in a large number of animals. The striking feature of the experiments was the almost uniform regularity with which certain organs were attacked. Lesions were found more frequently in the stomach, lungs, skin and endocardium than in the appendix. The entire gastro-intestinal tract was commonly the seat of hemorrhages and presented this picture in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. Hemorrhages were also noted in the thymus, muscle, pericardium, pleura, and periarticular tissues and eye, in the order named. Almost without exception the spleen was enlarged, with tense capsule and a soft, deeply-colored pulp. Vegetative endocarditis was found in thirteen rabbits. Where there was no hemorrhage, acute lesions were found at times in the myocardium, liver, kidney and skeletal muscles. Sometimes these areas could be recognized in the gross as small yellowish foci. The joint fluid of the knees was frequently cloudy, or the synovial lining quite pink, and the organisms were recovered from these in forty-eight rabbits. Cultures made from the brain in forty-six rabbits gave eight positive results. Twenty-one of these animals showed small petechiae in the lining of the lateral ventricles, and five of the animals showed small hemorrhages in the white matter of the cord. Ten positive cultures were obtained from the gall-bladder. From this brief description it is evident that the injection of micro-organisms into rabbits' veins produced a widespread infection, and in this article we wish to discuss in detail the lesions observed.

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MATERIAL AND METHODS

The material for this work was selected with a view to determine the effect of organisms from certain sources on rabbits' appendixes. All of the organisms from the different materials were studied in an effort to gain information on the elective tissue affinity of organisms. The material for this work was obtained from appendixes, from the tonsils of patients having appendicitis, from several pairs of tonsils and adenoid tissue removed in the children's clinic, from tonsils of fracture patients otherwise healthy, and pus from an infected hand. Among the appendixes there were included two normal appendixes, two acute ulcerative appendixes, three acute gangrenous appendixes, three chronic appendixes, peritoneal fluid in one case of appendicitis and pus from an abscess in an abdominal incision following an operation for acute gangrenous appendicitis. The tonsils studied consisted of those from five of the patients having appendicitis, and those of thirteen patients not suffering with this disease; of the latter group, ten were from patients with fractures, but otherwise well, while the remaining three consisted of tonsils removed from children affected with chronic tonsillitis. A mass of adenoid tissue from one of the latter three was also used for culture. The details concerning the method of making the cultures is contained in the paper entitled "Experimental Appendicitis." The majority of the animals received doses varying from 15 to 75 c.c. of the original growth; however, at times the entire sediment from 150 c.c. of the original growth was injected into one animal. The individual variation in resistance among the rabbits was a marked feature, in that some of the animals which received a small dose developed a severe bacteremia with many lesions, while other rabbits inoculated with a larger dose of the same material lived, and when killed revealed but few alterations in their organs. The organisms used for these experiments included hemolytic and nonhemolytic streptococci, pneumococci, staphylococci, *B. mucosus capsulatus* and *B. coli*. Fifty-eight animals received cultures containing hemolytic streptococci; of this number there were *Streptococcus pyogenes*, 39; with *S. infrequens*, 6; with *S. anginosus*, 3; and with *S. subacidus*, 10. Forty-three rabbits treated with material containing green streptococci were divided in the following way: 32 with *S. salivarius*, 3 with *S. mitis*, 6 with *S. equinus*, and 2 with *S. fecalis*. With the streptococci it was found that rabbits inoculated with hemolytic organisms developed a more severe type of bacteremia. Twelve rabbits were treated with material including organisms of the capsulated gram-negative group of bacilli, and five received material containing *B. coli*. Six animals were injected with material from which a staphylococcus was isolated as the principal organism, while

one rabbit received an injection of a culture of pneumococci. Owing to the large dosage, most of the animals died within twenty-four hours; and those which survived the inoculation were chloroformed at varying intervals not exceeding five or six days. Of the 125 rabbits used for these experiments, eighty-one died and forty-four were chloroformed. During these experiments our attention was particularly directed to an effort to reproduce appendicitis similar to that described by Rosenow,[1] in which he attributes an elective affinity to streptococci,

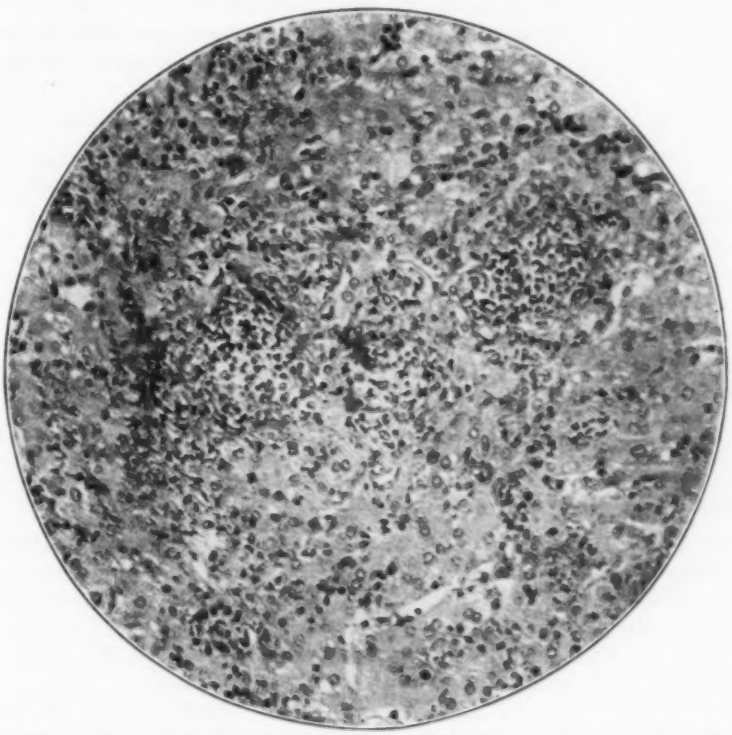

Fig. 1.—Animal 53; liver; *Streptococcus anginosus;* showing focal necrosis.

staphylococci, and *B. coli* isolated from the teeth, tonsils or appendix in individuals suffering with this malady. Consequently, as prescribed by him, we administered large doses of the isolated organisms both from the original material and after animal passage. Routine necropsies were made on all animals as soon as death was discovered, or

1. Rosenow: Jour. Infect. Dis., 1912, **11,** 210; idem., Jour. Infect. Dis., 1914, **14,** 61.

immediately on chloroforming. Cultures were made routinely from the heart's blood, knee joints and gallbladder, and sections of all the organs were fixed in Zenker's fluid and formaldehyd solution for microscopic study.

ORGANISMS STUDIED

As previously stated, all of the organisms isolated from the different sources were employed for inoculation. The sediment from each original growth was used either in whole amount or divided doses. Consequently, many of the rabbits received a mixture of organisms. At the time of inoculation, human blood agar streak plates were made in an effort to determine the nature of the organisms

TABLE 1.—

Organisms Injected	No. of Animals	Stomach	Appendix	Duodenum	Small Intestine
Pneumococcus	1	1	0	0	0
B. Friedländer	1	1	1	1	1
B. acidi lactici	10	9	8	7	9
B. lactis aerogenes	1	1	0	1	1
B. coli communis	5	5	2	3	2
Staphylococcus	6	3	5	3	3
Total	24	20	16	15	16

TABLE 2.—PERCENTAGE OF LESIONS—

Organisms Injected	No. of Animals	Stomach	Appendix	Duodenum	Small Intestine
Streptococcus hemolyticus	56	38 (69%)	30 (52%)	19 (32%)	17 (30%)
Streptococcus viridans	43	27 (63%)	16 (37%)	19 (44%)	5 (11%)
General organisms	24	20 (83%)	16 (66%)	15 (62%)	16 (66%)
Total	125	85 (68%)	62 (49%)	53 (42%)	38 (30%)

administered. After isolation from the original material, or after animal passage, pure cultures of the organisms were employed. Following the use of the original mixture, our attention was particularly directed to the streptococci contained in the original material and also those obtained from the animals at necropsy. These organisms were classified and studied according to the methods described by Holman.[2] Although as already stated, we were chiefly interested in the effect of

2. Holman: Jour. Med. Research, 1916, **34,** 377; idem., Jour. Med. Research, 1916, **35,** 151.

the streptococci contained in the materials studied, we, nevertheless, have quite a group of animals which were injected with other types of organisms. Following this we have a number of animals which, although injected with material containing organisms in addition to the streptococci, nevertheless exhibited lesions which were quite characteristic for the streptococci.

DISCUSSION OF THE BACTERIOLOGIC RESULTS

With the administration of mixtures of organisms, varying degrees of infection were noted. Although depending in part on the dose given, it was frequently found that animals which received a small

GENERAL ORGANISMS

Heart		Joint	Muscles		Periart.	Endocardium		Kidney	Thymus
Hemor.	Infilt.		Hemor.	Infilt.		Hemor.	Infilt.		
0	0	0	0	0	1	1	0	0	1
0	0	0	0	0	0	1	0	0	0
0	0	8	2	2	0	8	0	0	4
0	0	1	0	0	1	1	0	0	1
0	0	4	0	0	0	4	0	0	4
1	2	0	0	0	0	2	2	0	2
1	2	13	2	2	2	17	2	0	12

—SHOWING ALL TYPES OF ORGANISMS

Heart		Joint	Muscles		Periart.	Endocardium		Kidney	Thymus
Hemor.	Infilt.		Hemor.	Infilt.		Hemor.	Infilt.		
6	10 (27%)	28 (48%)	6	3 (15%)	8 (14%)	33	3 (62%)	4 (7%)	24 (41%)
5	14 (44%)	7 (10%)	6	0 (14%)	5 (11%)	18	10 (68%)	7 (16%)	11 (25%)
1	2 (12%)	13 (54%)	2	2 (16%)	2 (8%)	17	2 (79%)	0	12 (50%)
12	26 (30%)	48 (38%)	14	5 (15%)	15 (12%)	68	15 (60%)	11 (8%)	47 (37%)

dose were more seriously affected than other animals that had received a larger dose of the same material. Another point worthy of note was the ultimate effect a certain organism or mixture of organisms had on different animals. The degree of bacteremia varied to a great extent, and the same organisms were not necessarily recovered from all post-mortem cultures of a given number of animals injected with the same material. Furthermore, in the post-mortem cultures organisms were sometimes found other than those isolated from the original material. Pneumococci and capsulated gram-negative

bacilli were found on a number of occasions where these organisms were not isolated from the original material. Although realizing the difficulty of making an absolutely correct cultural diagnosis, we feel that we are justified in emphasizing the importance of at least considering these points in a serious light and not being too hasty in believing that some organism which we found in the mixture had changed its character after injection into the rabbit's veins. Holman[2] has commented on the invasion of organisms from normally infected sources when animal bodies are in a lowered state of resistance. Again, different animals react differently to the same material, and we have found varying results in post-mortem cultures taken from animals injected with the same material. This variation was found in those animals which were injected with mixtures containing several organisms. Animals injected with pure cultures of the same organism did not show this variation so frequently; however, occasionally the cultures in one animal would show the organisms injected, while those in the other animal were sterile. All of the animals injected did not show a bacteremia. However, a large number of the animals died as rapid a death as those which showed organisms in the post-mortem cultures. This must undoubtedly be attributed to the severity of the toxemia produced. As previously stated, eighty-one of the rabbits died. Of this number, forty-eight rabbits had a positive blood culture at necropsy. Hemolytic streptococci were found 19 times, including *S. anginosus*, 3; *S. pyogenes*, 14, and *S. infrequens*, 2. Green streptococci were isolated 11 times, including *S. salivarius*, 7; *S. mitis*, 2, and *S. equinus*, 2. The *Pneumococcus* was found in the blood of one rabbit. Capsulated gram-negative bacilli were isolated 17 times, including *B. Friedländer*, 3; *B. acidi lactici*, 12, and *B. lactis aerogenes*, 2. *B. coli communis* was found 5 times, *B. coli communior*, 1, and *B. proteus vulgaris*, 1. Six of these animals had more than one organism in the blood. Hemolytic streptococci were found in cultures from the knee joint 25 times, including *S. pyogenes* 20, and *S. anginosus* 5. Green streptococci were isolated 7 times, all of which were *S. salivarius*. Capsulated gram-negative bacilli were obtained 14 times from the knee joint, including *B. Friedländer*, 2; *B. acidi lactici*, 9, and *B. lactis aerogenes*, 3. *B. coli communis* was cultured 3 times. Cultures made from the brain in forty-six rabbits showed *S. salivarius* 1 and *S. pyogenes* 7 times. Cultures made from the gallbladder showed *B. acidi lactici*, 6; *B. coli communis*, 2; *S. equinus*, 1, and *B. Friedländer*, 1. Along with the cultures just described, material was also taken from the pleura, pericardium and peritoneum, where these membranes showed definite signs of inflammation in the gross, with the result that a causative factor was found in most instances. Streptococci

were isolated from the appendix and glands about the cecum, as well as from the periarticular tissues and muscles. Where the organisms were not obtained in culture, they were frequently demonstrated in gram-stained sections. Thus, we found a wide dissemination of organisms in animals injected for the express purpose of demonstrating a certain elective quality for a particular tissue in these animals, with the result that lesions were found in other organs in a very appreciable percentage of cases.

Fig. 2.—Animal 53; kidney; *Streptococcus anginosus;* showing embolus of cocci and glomerulus surrounded by polymorphonuclear leukocytes, endothelial cells and lymphocytes. There is also interstitial infiltration of these cells.

A survey of the bacteriologic examination of these animals indicated that in a bacteremia the organisms are quite generally distributed in all parts of the body. In case of the hemolytic streptococci, positive cultures were obtained post mortem nineteen times from the blood and twenty-five times from the knee joint. Rosenow[1] has called attention to the frequency with which hemolytic streptococci injected intravenously can be recovered from the joint cavities, a

condition which, no doubt, is the result of the interaction of two factors, the one the invasive power of the organism itself and the other, the very favorable nidus which the streptococcus finds. Green streptococci were cultivated eleven times from the blood and seven times from the knee joint. Here there is a slight advantage for the blood cultures which, no doubt, depend on the viability of the organisms, and further on the fact that green streptococci have more difficulty in attacking an uninjured tissue than do the hemolytic organisms. Of the other organisms which produced a severe reaction in the animals, the capsulated gram-negative bacilli were the most important. These organisms were isolated from the blood seventeen times and from the knee joints fourteen times.

Dick[3] has commented on the apparent affinity of capsulated gram-negative bacilli for the joints. Here we must bear in mind the marked tenacity for life exhibited by these organisms and the very severe general infections which are at times observed in humans due to these organisms.

DESCRIPTION OF AND DISCUSSION ON LESIONS

The lesions observed in these experiments consisted of two types, hemorrhagic and exudative. There was a wide distribution of hemorrhages in the organs of the animals. In many animals hemorrhages were found in all parts of the body. As listed in the paper entitled "Experimental Appendicitis," the lesions which were most pronounced were those observed as hemorrhage. Hemorrhages appeared more often in the stomach, lungs, skin and endocardium than in the appendix. The gastro-intestinal tract showed hemorrhages in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. The thymus, muscle, pericardium, pleurae, periarticular tissues and eye showed hemorrhages in the order named. These hemorrhages were usually observed as small, discrete areas. There were at times, however, quite diffuse hemorrhages about the joints and into the muscles of the extremities as well as other of the skeletal muscles. Microscopically, they were observed as interstitial collections of blood cells, as in the muscles, while again diffuse hemorrhages were found in the follicles of the appendix. The thymus very often showed massive hemorrhage replacing the structure of parts of the gland. At times infiltration of leukocytes occurred about and through the hemorrhage. The blood vessels in the vicinity of the hemorrhage commonly showed plugs of organisms without evidence of inflammatory reaction. The protocol of Rabbit 63 will serve to illustrate the extensive character of the hemorrhagic lesions which

3. Dick: Jour. Infect. Dis., 1914, **16,** 176; idem., Jour. Am. Med. Assn., 1917, **68,** 622.

frequently occurred. This animal was injected with the sediment from 150 c.c. of a twenty-four-hour growth of *B. acidi lactici* obtained from an appendix. The animal died in one and one-half hours in a violent convulsion. At necropsy there were extensive bright red blotchy hemorrhages into the skin over the entire back. The conjunctiva bordering on the cornea and extending into the reflections of the bulbar conjunctiva showed many bright red hemorrhages. These varied in size from fine petechiae to quite large, irregular blotchy areas.

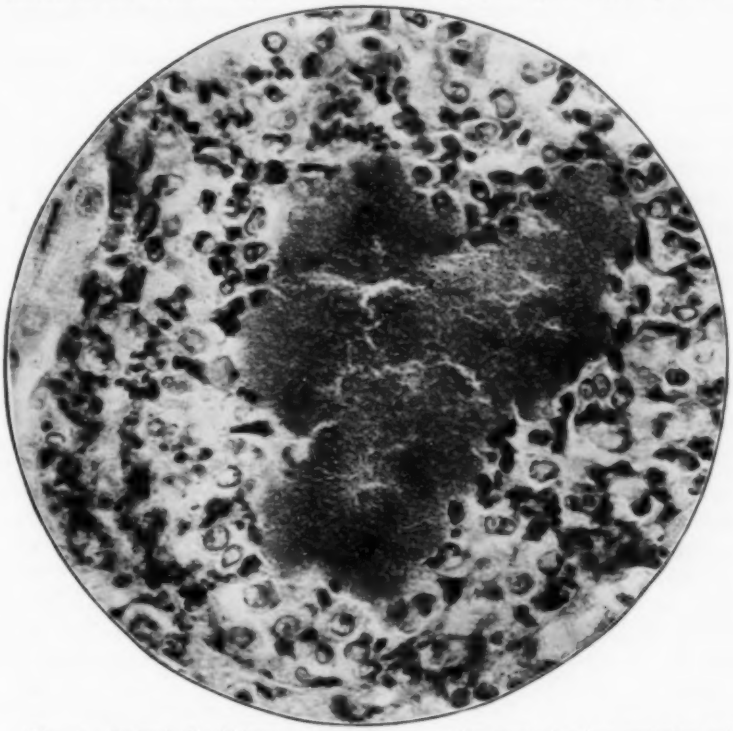

Fig. 3.—Animal 64; kidney; *Streptococcus salivarius;* showing embolus of cocci in the glomerulus with an infiltration of large swollen endothelial cells.

The pleural cavities were free from fluid and there were no hemorrhages into the pleura. There were, however, closely aggregated, bright red, discrete areas in the soft tissue of the anterior mediastinum, some of which were quite thick and suggested considerable leakage of blood, although there was no free blood in the mediastinal space. There was no hemorrhage into the thymus. The lungs were intensely congested and showed blotchy hemorrhages beneath the pleura. The endocardium of the left ventricle showed many discrete and confluent

bright red hemorrhages. The omentum contained many bright red hemorrhages. Some of these were blotchy, while others were very prominent and formed small blood blisters. These hemorrhages measured from 0.2 to 0.5 cm. in diameter. There were a few bright red hemorrhages into the mesentery. The stomach showed several small chocolate colored areas in the mucosa of the cardia. These did not appear to be of recent origin. In the first half of the duodenum there

TABLE 3.—

Organisms Injected	No. of Animals	Stomach	Appendix	Duodenum	Small Intestine
S. pyogenes	28	19	15	7	5
S. subacidus	10	5	2	2	1
S. anginosus	3	3	1	1	1
S. infrequens	2	1	1	1	0
S. pyogenes—S. salivarius	5	3	3	2	3
S. pyogenes—pneumococcus	6	4	5	4	3
S. infrequens—B. Friedländer	4	3	3	2	4
Total	58	38	30	19	17

TABLE 4.—

Organisms Injected	No. of Animals	Stomach	Appendix	Duodenum	Small Intestine
S. salivarius	31	19	13	13	4
S. equinus	6	4	2	3	0
S. fecalis	2	2	0	2	0
S. mitis	3	1	1	1	1
S. salivarius—S. equinus	1	1	0	0	0
Total	43	27	16	19	5

was no change. However, from here on there was a diffuse speckling of the bowel with purpuric spots. These were visible equally well from the serosa and mucosa. In the midportion of the ileum there was an area of hemorrhage into the wall measuring 0.5 cm. in diameter. There were many smaller pinpoint-sized areas scattered diffusely in the bowel wall. Peyer's patches were markedly involved, presenting diffuse areas of hemorrhage which extended deep into their substance. There was a diffuse speckling of the cecum just beyond the ileocecal valve. The appendix mucosa was peppered over with a great number of small discrete and confluent hemorrhages which were just beneath

the mucosal surface. The large bowel and upper rectum showed several areas of hemorrhage in the mucosa. All of the animals injected with *B. lactis aerogenes* and *B. acidi lactici* showed a similar picture, although Rabbit 63 was the only animal which died so rapidly. Although microscopically these hemorrhages were observed either as interstitial or more diffuse infiltrations of red cells which replaced tissue, there were, nevertheless, occasionally inflammatory infiltrations.

—Streptococcus Hemolyticus

Heart		Joint	Muscles		Periart.	Endocardium		Kidney	Thymus
Hemor.	Infilt.		Hemor.	Infilt.		Hemor.	Infilt.		
4	9	14	2	2	2	15	1	3	9
0	0	4	0	0	1	3	0	0	3
0	1	0	1	0	1	2	0	1	2
0	0	0	1	1	0	1	1	0	0
0	0	4	1	0	2	2	0	0	3
2	0	4	1	0	1	6	0	0	4
0	0	2	0	0	1	4	1	0	3
6	10	28	6	3	8	33	3	4	24

—Streptococcus Viridans

Heart		Joint	Muscles		Periart.	Endocardium		Kidney	Thymus
Hemor.	Infilt.		Hemor.	Infilt.		Hemor.	Infilt.		
4	13	7	5	0	4	13	6	6	9
1	1	0	1	0	1	2	1	1	1
0	0	0	0	0	0	1	0	0	1
0	0	0	0	0	0	1	2	0	0
0	0	0	0	0	0	1	1	0	0
5	14	7	6	0	5	18	10	7	11

With the streptococci, hemorrhage was a constant feature which was more marked with the hemolytic streptococci. Here, however, in contradistinction to the animals treated with capsulated gram-negative bacilli, exudative lesions were more apt to occur. Although very often the latter lesions were not discovered except by microscopic examination, they were, nevertheless, very clearly seen in the gross in some animals. Rabbit 157 was injected with the sediment from 75 c.c. of a twenty-four-hour growth of *Streptococcus pyogenes*. Five days later the animal was very sick and was chloroformed and necropsied immediately. There were yellowish white streaks in most of the skeletal

muscles. These were observed as tiny spinales running in the direction of the muscle fibers. They were compact and no material could be squeezed from them. On cross section they were seen as small round yellowish dots. The same type of nodules were found diffusely scattered through the heart muscle and kidney. There was a pea-sized warty nodule of yellow fibrin on the mitral valve which almost closed the opening. Fading pinkish red areas were found in the mucosa of the small intestine and appendix. *Streptococcus pyogenes* was isolated from the muscle. Rabbit 64 was injected with the sediment from 150 c.c. of a twenty-four-hour growth of *Streptococcus salivarius*. Two days later the animal died. Necropsy was performed at once. There were blotchy hemorrhages into the skin of the back and sides. Circumscribed, deeply-colored areas were found in the lungs as well as blotchy hemorrhages into the pleura. The heart showed some small petechiae in the pericardium, with many tiny pinpoint white dots shining through. Similar small dots could be seen through the endocardium and on section they were observed as millet-like bulging masses on the cut surface. They were solid and no material could be squeezed from them. There was a warty fibrinous deposit on the tricuspid valve. The stomach showed many fine petechial dots in the mucosa of the cardiac end. A similar condition was noted in the first part of the duodenum and also in the appendix. The kidneys showed a very marked bright red streaking of their cortexes. The intermediate zone was deeply congested and irregular in outline. There were many tiny white dots distributed throughout the cortex and for some distance into the medulla. These were similar in appearance to the foci observed in the heart muscle. *Streptococcus salivarius* was isolated from the heart blood and knee joint. Although these two animals were injected with different members of the streptococcus group, the distribution of the lesions was quite similar, save for the muscle, and microscopically these foci had much in common. These lesions will be described in detail later with special reference to the animals and ones showing similar lesions.

One hundred and one animals were injected with streptococci. Exudative lesions were observed in the heart twenty-four times, in the kidney eleven times and in the muscle three times. Of the rabbits which showed a myocarditis, 13 received *S. salivarius* and 10 *S. hemolyticus*, including *S. pyogenes*, 9, and *S. anginosus*, 1. One rabbit was treated with *S. equinus*. The two rabbits injected with staphylococci showed abscesses in the myocardium. Changes noted in the kidney were divided in the following way: 6 with *S. salivarius*, 1 with *S. equinus* and 4 with *S. hemolyticus*, including *S. pyogenes*, 3, and *S. anginosus*, 1. The skeletal muscle lesions were produced twice by

S. pyogenes hemolyticus and once by *S. hemolyticus infrequens*. There were two other rabbits which showed exudative muscle lesions, both of which were injected with *B. acidi lactici*. However, in gram-stained sections, both of these lesions showed gram-positive cocci in the neighboring vessels. Of the animals injected with streptococci, seven showed exudative lesions in both the heart and kidney, while one of these showed lesions in heart, kidney and muscle. The latter animal was

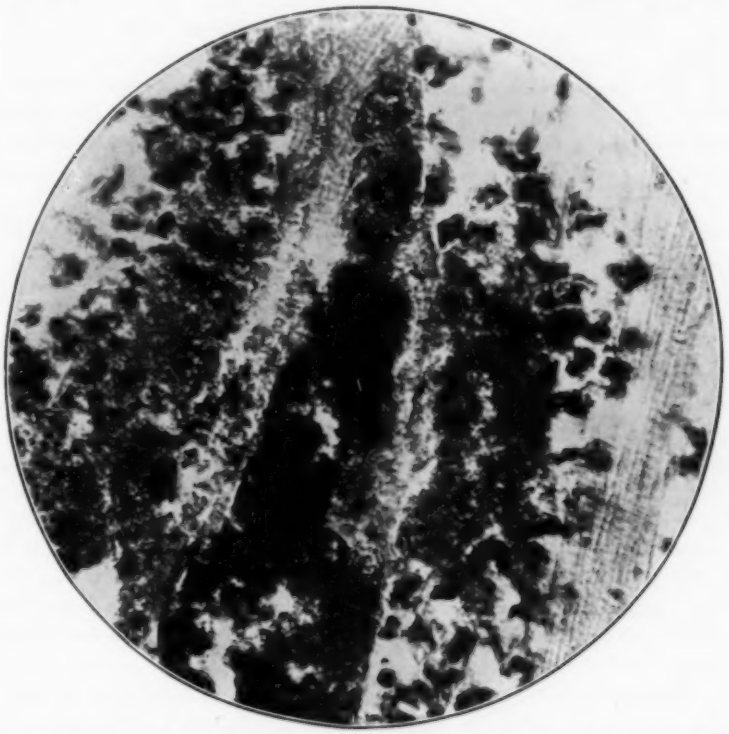

Fig. 4.—Animal 64; heart muscle; *Streptococcus salivarius;* showing embolus of cocci surrounded by large swollen endothelial cells, some of which contained phagocyted cocci.

inoculated with *S. pyogenes*. Of the remaining 6 which showed lesions in both heart and kidney, 4 received *S. salivarius*, while the other 2 were inoculatetd, respectively, with *S. anginosus* and *S. pyogenes*. As previously stated, the prominent features observed in these animals was the occurrence of discrete or confluent hemorrhages. The size of the doses given caused a rapid death of most of the animals, while the remaining members of individual groups were chloroformed either at

the time or within a day or two for comparison. The high percentage of hemorrhage observed in our animals corresponds closely to the results of Rosenow, who believes such hemorrhages are the forerunners of exudative lesions. In our animals the hemorrhages occurred in the majority of cases without evidence of inflammatory infiltration. Small vessels in the vicinity of these areas were frequently found plugged with cocci or bacilli, apparently without damage to the vessel as far as evidenced by an inflammatory reaction. The effect of the toxins of the organisms on the capillary walls must be an important factor. However, from the foregoing evidence the mechanical effect of these plugs on the vessel walls must also be a point of first importance. When the amount of sediment given is considered, the rabbit has received a considerable bulk of foreign matter into his vessels, which, no doubt, has a decided damaging effect on delicate capillary structures, apart from the injury done by the activity of the organisms and their toxins. We believe, however, that the large doses employed caused an overwhelming infection which was evidenced in the main by a fairly constant distribution of hemorrhages in the several parts of the animal's body.

Heart Valves.—Thirteen rabbits showed vegetative lesions and in two others the valves contained small discrete hemorrhages. Deposits of fibrin were found on the mitral and on the tricuspid valve, each six times. In one rabbit vegetative lesions were found on both the mitral and tricuspid, while in the last case there was a mural vegetation in the right ventricle. Eight of these rabbits were injected with green streptococci, including *S. mitis,* 2; *S. salivarius,* 5, and *S. equinus* and *salivarius.* Two received injections of hemolytic streptococci, 1 *S. pyogenes,* and the other *S. infrequens.* Of the remaining three, two were given straphylococci and the third *B. acidi lactici.* Of the two rabbits exhibiting hemorrhage into the valves, the first was inoculated with *S. salivarius* and the second with *S. equinus.*

Endocarditis has been produced by a variety of organisms, and it is generally known that the production of the lesion is associated with infection. Fulci[4] was unable to produce an ulcerative or vegetative endocarditis by using sterile toxins, even when associated with mechanical or chemical injury. This observation was in accordance with the work of Rosenback,[5] done years before, who said that mechanical injury did not of itself produce inflammatory changes in the valves. So, as Orth[6] has pointed out, the presence of micro-organisms circulating in the blood is essential for the production of the condition.

4. Fulci: Ziegler's Beit. z. path. Anat. u. z. allg. Path., 1908, **44,** 349.
5. Rosenback: Arch. f. exper. Path. u. Pharmakol., 1878, **9,** 1.
6. Orth: Virchows Arch. f. path. Anat., 1886, **103,** 300 and 333.

About this same time Ribbert[7] succeeded in producing endocarditis by injecting emulsions of potato and staphylococci. However, since this time, many other workers have succeeded in producing endocarditis without first causing injury to valves. Saltykow[8] succeeded by using cultures of *Staphylococcus pyogenes aureus*. Lissauer[9] found endocarditis in two of twenty rabbits which received injections of a coccus

Fig. 5.—Animal 116; kidney; *Streptococcus equinus;* showing dense interstitial infiltration of lymphocytes.

like *Staphylococcus albus*. Of the various organisms associated with endocarditis, streptococci are the most frequent. However, other organisms are found often enough to be given worthy consideration. In forty-three cases of infectious endocarditis, Harbitz[10] found 7 streptococci, 5 pneumococci, 8 staphylococci, 3 not classified and 10 healed.

7. Ribbert: Fortschr. d. Med., 1886, **4**, 1.
8. Saltykow: Virchows Arch. f. path. Anat., 1912, **209,** 126.
9. Lissauer: Centralbl. f. Path., 1912, **23,** 243.
10. Harbitz: Deutsch. med. Wchnschr., 1899, **121.**

In the human, infectious endocarditis due to streptococci has been described by a number of authors. Poynton and Paine[11] concluded that the endocarditis in rheumatism is due to the organisms of rheumatism, and that the tonsils in rheumatic cases harbor the *Micrococcus rheumaticus*. Libman[12] has described a type of subacute bacterial endocarditis and he and Cellar have described in detail the organism associated with this disease. Osler,[13] Schottmüller[14] and Horder[15] have described a similar type of disease. Billings[16] in a report of 14 cases of infectious endocarditis found pneumococcus 11 times and streptococci 3 times. The findings coincide with the belief of Rosenow, who is convinced that the organisms responsible for endocarditis are modified pneumococci, which readily form clumps, thus facilitating the production of emboli, which is the primary step in endocarditis according to his interpretation. Experimentally, streptococci have been employed by many authors for the production of endocarditis in laboratory animals. Beattie[17] produced endocarditis and polyarthritis in animals injected with *Micrococcus rheumaticus*. These observations have been substanttiated by the work of Poynton and Paine,[10] Cole,[18] Walker,[19] Libman and Cellar,[12] and others. Horder[15] found that streptococci cultivated from the blood in cases of chronic infectious endocarditis, as well as allied streptococci cultivated from the throat and feces, are prone to produce endocarditis in animals. Rosenow found that streptococci isolated from cases of endocarditis showed a special affinity for the endocardium of laboratory animals. He found that animals injected with these organisms gave 84 per cent. endocarditis as against only 14 per cent. in animals inoculated with streptococci from other sources. Further than this, the disease was always an embolic process and was caused by modified pneumococci. As against these results, Henrici[20] concluded that streptococcal endocarditis usually develops by implantation on the surface of the valve. The latter author observed no specific difference in the affinities of the various

11. Poynton and Paine: Lancet, London, 1910, **178,** 1524.
12. Libman: Tr. Assn. Am. Phys., 1910, **25,** 5. Libman and Cellar: Am. Jour. Med. Sc., 1910, **140,** 516.
13. Osler: Brit. Med. Jour., 1885, **1,** 467, 522, 577 and 607; idem., Practitioner, London, 1893, **50,** 183.
14. Schottmüller: München. med. Wchnschr., 1903, **50,** 849 and 909; 1910, **57,** 617.
15. Horder: Quart. Jour. Med., 1908-1909, **2,** 289.
16. Billings: The Archives Int. Med., 1909, **4,** 409.
17. Beattie: Jour. Med. Research, 1906, **14,** 399; idem., Edinburgh Med. Jour., 1908, **13,** 391.
18. Cole: Jour. Infect. Dis., 1904, **1,** 714.
19. Walker: Brit. Med. Jour., 1907, p. 1233.
20. Henrici: Jour. Infect. Dis., 1916, **19,** 572.

classes of streptococci for the heart valves. Fox[21] inoculated rabbits with a freshly isolated strain from the tonsil of a girl with rheumatism, four times in twenty days and found fibrinous mitral endocarditis, also myocarditis. This author also gave a rabbit eight doses of a streptococcus pyogenes from a case of puerperal sepsis and found mitral endocarditis as well as myocarditis. He concluded that all cases of valvular disease have primary myocarditis present at the base of

Fig. 6.—Animal 120; heart muscle; *Streptococcus salivarius;* arteriole in heart muscle showing acute endarteritis with puffing of the intima and infiltration of endothelial cells, lymphocytes and leukocytes.

the valve, and that this condition leads to an edema of the valve which permits of endocarditis.

The lesion observed on the valves of our animals consisted either of subendothelial hemorrhages or vegetations. Microscopic examination of the latter structures showed masses of cocci surrounded by fibrin with dense collections of leukocytes and lymphocytes. The endothelial covering of the valve was missing where the vegetation was

21. Fox: Centralbl. f. Path., 1913, **24,** 529.

adherent and fibrin and inflammatory cells with red blood cells extended into the deeper layers of the valve. In one case a small nodule near the edge of the valve closely resembled the lesions observed beneath the mural endocardium, which are described under heart muscle. Aside from the changes described subendocardial hemorrhages were found in sixty-eight animals.

Heart Muscle.—In acute rheumatic fever there is a type of myocarditis which is considered as specific for infection with the rheumatic virus. These bodies have been termed Aschoff-Geipel bodies and are most commonly noted in the walls of the left ventricle beneath the endocardium and pericardium and also frequently about the bases of the valves. These areas were first described by Aschoff,[22] who found that there was a proliferation of cells arranged in the form of a fan or rosette, making up nodules which occurred near the small or medium sized vessels, and often in close relation to the adventitia of these vessels. The lesions consist of large cells which have one or more polymorphous nuclei and the center of the nodule is faintly staining as if composed of necrotic masses of protoplasm. Beside the so-called giant cells, the lesions include large and small lymphocytes, with the latter more numerous at the periphery. These bodies have since been described by Wachter,[23] Thorel,[24] Coombs,[25] Fraenkel,[26] Douglas,[27] Low,[28] Thalheimer and Rothschild,[29] and many others. Closely allied or similar lesions have been produced experimentally by a number of workers. Bracht and Wachter[30] observed submiliary nodules in three or four cases giving a rheumatic history. *S. mitis* was isolated from the heart's blood in two of the cases, and when this organism was injected into rabbits they failed to find Aschoff bodies in the hearts of the rabbits. They found, however, a focal myocarditis which consisted of patchy lymphocytic infiltration. They considered these results significant, however, in that rabbits inoculated with *S. pyogenes* showed miliary abscesses in the heart muscle. Jackson[31] compares the nodules produced experimentally with those found in human rheumatic hearts. This author inoculated rabbits with a hemolytic streptococcus which was obtained from a milk borne epidemic of sore throat. The myocar-

22. Aschoff: Verhandl. d. deutsch, path. Gesselch., 1904, **8,** 46.
23. Wachter: München. med. Wchnschr., 1908, **55,** 1101.
24. Thorel: Lubarsch. Ostertag., 1915, **17,** 435.
25. Coombs: Jour. Path. and Bacteriol., 1911, **15,** 490; idem., Lancet, London, 1909 **1,** 1377.
26. Fraenkel: Ziegler's Beit. z. path. Anat. u. z. allg. Path., 1912, **52,** 597.
27. Douglas: Jour. Path. and Bact., 1913, **18,** 119.
28. Low: Ziegler's Beit. z. path. Anat. u. z. allg. Path., 1910, **49,** 1.
29. Thalheimer and Rothschild: Jour. Exper. Med., 1914, **19,** 417, and 444.
30. Bracht and Wachter: Deutsch. Arch. f. klin. Med., 1909, **96,** 493.
31. Jackson: Jour. Infect. Dis., 1912, **11,** 243; 1913, **12,** 364.

dium contained small groups of cells which were quite uniformly distributed and occupied the space between one or more muscle fibers with the long axis parallel to the fibers. The most conspicuous cell in these areas was large, with large oval or round and sometimes irregular nuclei. These large cells often contained phagocyted streptococci. In addition to the larger cells, there were smaller cells with more deeply stained nuclei and a small amount of cytoplasm. These cells and a few

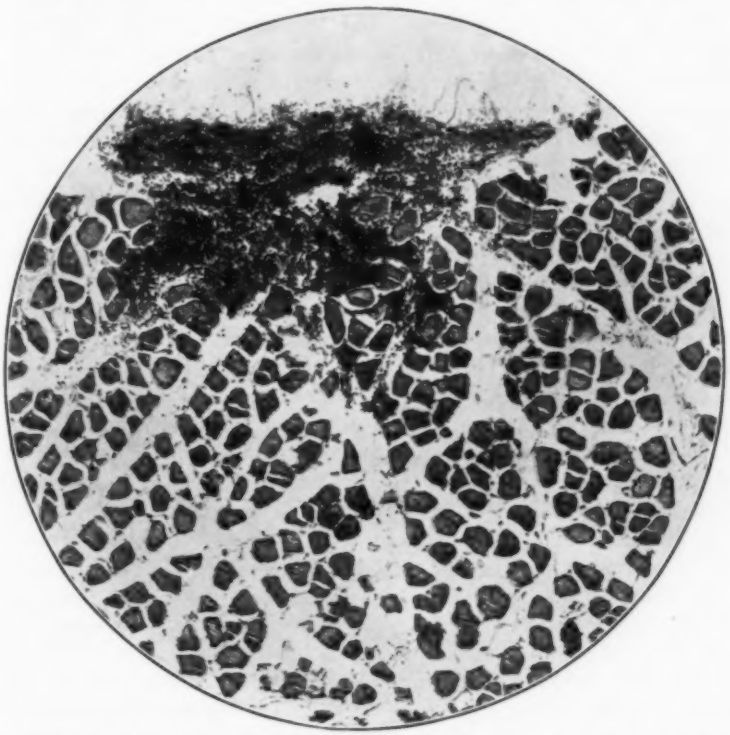

Fig. 7.—Animal 148; skeletal muscle; *Streptococcus infrequens;* showing hemorrhage.

leukocytes were irregularly disseminated throughout the area. Thalheimer and Rothschild[29] injected rabbits with streptococci from epidemic sore throat and had seven animals develop the usual pyogenic type of lesions caused by *S. pyogenes.* Along with an extensive degeneration and destruction of muscle associated with a leukocytic infiltration, mainly polymorphonuclear and great numbers of cocci, there were a few fusiform areas resembling somewhat those described by Jackson. There were no giant cells, however, and no typical Aschoff bodies.

They base their belief on the fact that the cells were not basophilic and that their protoplasm did not stain red with methyl-green pyronin. These same authors also treated rabbits with *S. mitis* and *S. rheumaticus* (Poynton and Paine) and found no evidence to indicate that the focal myocarditis produced was similar to the submiliary nodules of Aschoff. In two rabbits inoculated with *S. viridans*, Hartzell and Henrici[32] found proliferative lesions in the heart in which multinucleated giant cells were prominent, and which they believed were similar to Aschoff-Geipel bodies. In a later paper, Henrici[20] described lesions which in the general appearance of the cells, their basicity, their accumulation in fusiform masses between the muscle fibers, or in rosettes about the vessels, their frequent subendocardial position and the frequent occurrence of multinucleated giant cells, presented all the characteristics of the typical Aschoff-Geipel nodules. This author also found no difference in the affinity of hemolytic and nonhemolytic streptococci for the heart muscle.

The reactions in the heart muscle of our animals varied somewhat in that the changes noted did not always consist of the same type of cell reaction. In some of the specimens leukocytic infiltration formed the prominent feature, while in other specimens there was a proliferation of large endothelial cells. At times these changes were noted independently or in combination in the same specimen. Where the leukocytic infiltration was the main feature, there was invasion of these cells between the muscle fibers, plugging the small capillaries and lymph spaces, forming a patchy interstitial inflammation. At times the small arterioles presented an acute endarteritis with a puffing of the intima and an infiltration of inflammatory cells inside of the elastica interna. When the reaction advanced the bordering muscle cells were invaded, with the formation of multiple small abscesses throughout the heart muscle. These areas consisted either of dense collections of leukocytes or of necrotic masses surrounded by a zone of these cells. Areas of a light to deep blue granular material were at times seen replacing the heart muscle. These areas were frequently unattended by an inflammatory reaction and involved irregular sections of the muscle fibers. These were looked on as areas of calcification, in that a number of preparations took the silver nitrate stain. Masses of cocci were frequently found in the center of the foci described above. Where *S. salivarius* was used, another type of reaction was the rule. In many areas lymphocytes were the predominant cell, with a few leukocytes scattered throughout, while again small and large mononuclear cells were in greater numbers. At times rather large cells were arranged about the blood vessels and in small nodules beneath the endocardium

32. Hartzell and Henrici: Jour. Am. Med. Assn., 1915, **64**, 1055.

and about the bases of the valves. There was also a similar type of proliferation which at times took place about the necrotic areas. Where clumps of cocci occurred in these areas, they were often phagocyted by the surrounding cells. These cells were swollen or elongated, with deep staining round or irregular nuclei. The protoplasm of these cells was wide, with a marked tendency to basophilia. However, many cells had a fairly light protoplasm, with a more dis-

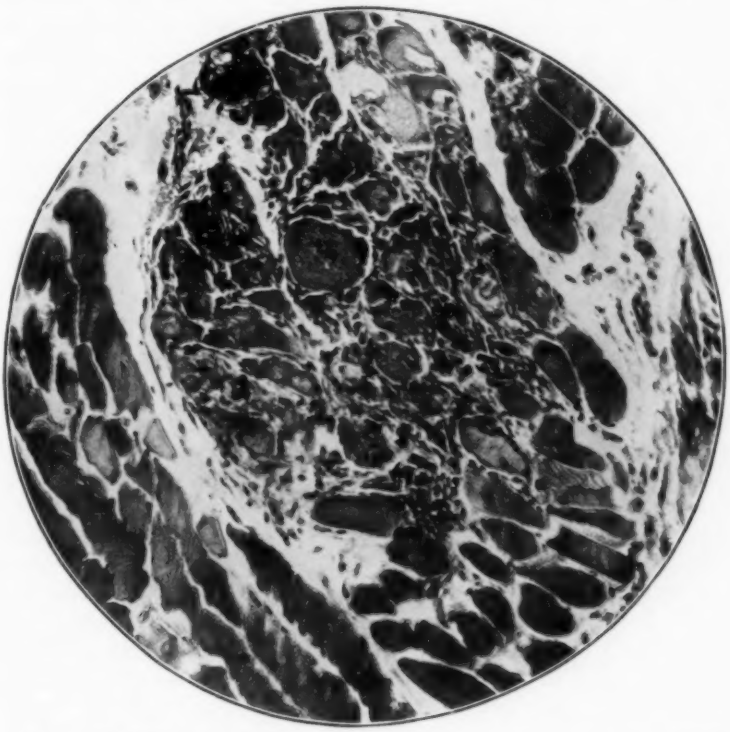

Fig. 8.—Animal 157; skeletal muscle; *Streptococcus pyogenes;* showing an exudative lesion consisting of endothelial cells, lymphocytes and a few polymorphonuclear leukocytes.

tinctly outlined nucleus, and in these, occasional nuclear figures were observed. Besides the lesions described, which were found in the rabbits injected with streptococci, hemorrhages were observed in twelve animals where there were no such lesions. The hemorrhages were found most commonly within the papillary muscles of the left ventricle. Table 2 shows the number of animals affected as well as the organisms used.

Joints.—Arthritis has been produced experimentally in animals by a number of investigators. Wassermann[33] isolated a diplococcus which he regarded as specific for rheumatism. Poynton and Paine[10] confirmed this view. Beattie[17] found that *Micrococcus rheumaticus* caused nonpurulent arthritis in 60 per cent. of the rabbits, and that these organisms differ from ordinary streptococci in this respect. Beattie and Yates[34] found that ten out of thirty-five strains of *S. viridans* isolated from various sources produced arthritis in rabbits. This was observed chiefly in the hind legs. Rosenow[2] isolated three types of streptococci in rheumatism, each of which could be readily converted into the other. These organisms produced arthritis in a small percentage and endocarditis in a high percentage of animals. The results of Thalheimer and Rothschild[29] are directly opposed to these, in that these authors found 50 per cent. arthritis and 7 per cent. endocarditis in animals injected with *S. mitis.* Furthermore, 45 per cent. of eleven animals injected with *S. rheumaticus* had arthrittis. These authors also found a variation in the abilitty of strains to produce arthritis, and concluded that the deduction of a distinct variety of species of streptococcus based on the power to cause arthritis in rabbits is unwarranted. Jackson[31] found no histologic differences in the joints of rabbits injected with various streptococci. Henrici[20] found that joint lesions were produced with equal frequency by both hemolytic and nonhemolytic strains. Schloss and Foster[35] used a hemolytic streptococcus from a throat and produced an arthritis suggestive of rheumatic arthritis. These authors asserted that chronic arthritis developed after repeated injections of this organism. Coombs, Miller and Kettle[36] produced proliferative lesions in the joints of rabbits inoculated with *S. rheumaticus.* Jackson[31] and Koch[37] have noted similar alterations in rabbits inoculated with a variety of streptococci. Dick[3] has twice reported the production of arthritis in rabbits and dogs with *B. lactis aerogenes.* This author also found that capsulated gram-negative bacilli isolated from the joints of persons suffering with rheumatoid arthritis showed a higher degree of affinity for the joints in animals. The arthritis varied from an acute hemorrhagic inflammation to a chronic deforming arthritis. In the more chronic cases the leukocytes present in the exudate were mostly of the round cell type. Rosenow has called attention to the frequency with which capsulated gram-negative bacilli are found in the joint cavities of animals injected experimentally with these organisms.

33. Wassermann: Berl. klin. Wchnschr., 1899, **36,** 638.
34. Beattie and Yates: Jour. Path. and Bacteriol., 1913, **17,** 538.
35. Schloss and Foster: Jour. Med. Research, 1913, **29,** 9.
36. Coombs, Miller and Kettle: Lancet, London, 1912, **2,** 1209.
37. Koch: Ztschr. f. Hyg. Infectionskr., 1912, **72,** 321.

Routine examination of the knee joints was conducted in all rabbits. Sections of the synovial membrane of the joints were not made. Cultures were made from all cases, and the joint fluid examined in a sufficient number of animals to determine the character of the exudate. The joint cavities were frequently distended with a thick, turbid, mucoid fluid, which, on examination, contained leukocytes, fibrin and bacteria. In case of infection with capsulated gram-negative bacilli,

Fig. 9.—Animal 157; skeletal muscle; *Streptococcus pyogenes;* showing marked destruction of muscle cells with a more acute reaction.

the joint fluid was frequently very sticky and stringy. In many animals the only sign of joint involvement was reddening of the synovial covering, or tiny petechiae into this membrane. Periarticular hemorrhages occurred in fifteen rabbits. Eight were due to hemolytic streptococci, five to *S. viridans,* one to *Pneumococcus* and one to *B. lactis aerogenes.* Hemolytic streptococci were isolated twenty-five times from the joint cavity and *S. viridans* seven times. Fourteen of fifteen animals injected

with capsulated gram-negative bacilli from several sources not including joints showed these organisms in the joints at necropsy. *B. coli communis* was found four times. All of the animals used received very large doses and lived only a day or so following the injection. Consequently, sufficient time had not elapsed for the development of varying degrees of reaction. We observed these conditions in the acute stage, and as a whole, found very little difference in the picture presented. From these results it would appear that the joint in an overwhelming infection is frequently the subject of attack by various organisms causing such infections.

Voluntary Muscles.—Rosenow[2] isolated streptococci from cases of muscular rheumatism in man and was able to reproduce similar lesions experimentally in animals by using the particular streptococci. Recently Henrici has reported the production of lesions in the voluntary muscles of rabbits by injecting them intravenously with various strains of streptococci.

The lesions observed in the muscles of our rabbits were of two kinds, either interstitial hemorrhages or areas of infiltration and necrosis, with, at times, areas of proliferative reaction. The first type was observed usually as small, well defined bright patches of hemorrhage. In several instances, however, the hemorrhage was very diffuse and in several rabbits involved all the muscles of an extremity. In the areas of necrosis with exudate, the muscle fibers were fragmented and formed hyaline-like granular bands. There was infiltration of lymphocytes and leukocytes with clumps of cocci in the neighboring vessels. At times there was an endothelial-like proliferation in the spaces between the muscle fibers. In one specimen these cells were arranged in and out among the muscle fibers in a wavelike or sweeping fashion. These cells varied in size and shape. Some were large, with large vesicular nuclei, while others were spindle shaped, with quite deep staining nuclei. The protoplasm was fairly abundant and moderately deeply stained. Where the muscle fibers were necrotic the proliferating cells were of the multinucleated, giant cell type. These muscle cells were hyaline-like to pale blue and some were fragmented. At times calcification was in progress in the necrotic muscle cells. In other places in this muscle, necrosis of muscle cells was the marked feature, with infiltration of leukocytes and the presence of cocci in the area. The lesions described above were noted in the gross as small spindle-shaped foci running in the long axis of the muscle fibers. On cross section they were observed as pinhead-sized, quite round, yellowish white dots scattered irregularly throughout the muscle. In one rabbit these areas were found in all of the skeletal muscles and the diaphragm. These observations resemble very closely those reported by Henrici.

Of the rabbits which showed exudative lesions in the muscles, two received *S. pyogenes hemolyticus* and one *S. infrequens*. Two other rabbits inoculated with *B. acidi lactici* showed degenerative necrotic areas with marked hemorrhage. Fourteen animals showed interstitial hemorrhagic lesions. Six were inoculated with green streptococci, including *S. salivarius*, 5, and *S. equinus*, 1. Four received pure cultures of hemolytic streptococci, including *S. anginosus*, 1; *S. pyogenes*, 2, and *S. hemolyticus infrequens*, 1. One rabbit was given a mixture of *S. pyogenes* and *S. salivarius*, and another *S. pyogenes* and *Pneumococcus*. The last two rabbits were treated with *B. acidi lactici*.

Kidneys.—Several types of nephritis have been produced experimentally in animals by the employment of streptococci. Klotz[38] used the various members of the *S. viridans* group and found lesions in the kidneys similar to those reported by Gaskell[39] and Baehr[40] in man. This author also declared that the associated inflammatory processes of perivascular arrangement found in the heart, liver, joint capsules and other tissues suggest a common mode of attack by these streptococci on many tissues. Lecount and Jackson[41] and Henrici[20] have described similar lesions in animals injected with different varieties of streptococci. The latter author found that the lesions were produced somewhat more frequently by hemolytic strains than by *S. viridans;* however, there was not observed any greater tendency of the former group to produce miliary abscesses.

Of the rabbits among our animals which showed kidney lesions, six were injected with *S. salivarius*, one with *S. equinus* and four with hemolytic streptococci, including *S. pyogenes*, 3, and *S. anginosus*, 1. These lesions were observed in the gross on several occasions as small yellowish white dots scattered through the cortex. Two of these animals showed vegetative endocarditis as well as kidney changes. One was injected with *S. pyogenes* and the other with *S. salivarius*. Seven rabbits had myocardial changes as well as kidney lesions. Four of these animals received doses of *S. salivarius*, two *S. pyogenes*, and the last *S. anginosus*.

Several grades of reaction were noted. A number of animals included in the foregoing group of eleven showed varying degrees of hemorrhage into the glomeruli, tubules and interstitial tissues. The cells of the glomerular tufts were very much swollen, so that the space was obliterated at times, while again the injury was so great that hemorrhage took place into the capsular space. Where there was

38. Klotz: Canad. Pract. and Rev., 1914.
39. Gaskell: Jour. Path. and Bacteriol., 1912, **16,** 283.
40. Baehr: Jour. Exper. Med., 1912, **14,** 330.
41. Lecount and Jackson: Jour. Infect. Dis., 1914, **15,** 389.

hemorrhage into the tubules, the lining cells were in some cases hyaline in character, with indistinct nuclei. The inflammatory reactions consisted either of interstitial perivascular infiltration of lymphocytes and a few plasma cells, or, as in one case, of the formation of minute abscesses in the intermediate zone. At times the cells of the perivascular spaces were swollen and proliferating. Still another type of reaction showed plugs of cocci in the glomeruli. The confines of the Bowman's capsules were still visible, with the cells of the tufts pressed against the wall of the capsule, showing several layers where the outlines of the cells were indistinct. About the embolus of the cocci, and also among the remains of the tufts, there were swollen, proliferating endothelial cells. Some of these large mononuclear cells contained phagocyted cocci. The nuclei of these cells were deeply staining and the protoplasm abundant. Lymphocytes and occasional leukocytes were observed in these areas. These lesions occurred following the injection of *S. viridans*. Concerning the other inflammatory changes described, no difference was noted in the relation of hemolytic and nonhemolytic streptococci to them.

Thymus.—This organ quite frequently showed petechial hemorrhages throughout its structure. These lesions were scattered widely in the swollen glandlike structure in the form of bright red spots varying in size from that of a pinhead to small blotchy patches.

Sections of the thymus showed varying degrees of hemorrhage into the lobules of the lymphoid tissue. The tiny capillaries were engorged and distended with red blood cells and they had often ruptured, allowing the blood to spread widely into the tissue. There was no inflammatory reaction associated with the hemorrhage. In some places large endothelial cells were lodged in the lymph spaces with, at times, a moderate proliferation of these cells. The structure of the gland was mostly swollen and edematous.

Liver.—Examination of the liver of these animals showed the presence of an exudative lesion twenty-nine times. Ten of these cases had been treated with hemolytic streptococci, including *S. subacidus*, 5; *S. pyogenes*, 3; *S. anginosus*, 1, and *S. infrequens*, 1. Of the remaining nineteen, sixteen had received strains of *S. viridans*, among which were *S. salivarius*, 11; *S. mitus*, 2; *S. fecalis*, 2, and *S. equinus*, 1. Two rabbits were injected with cultures of staphylococcus and one with *B. acidi lactici*.

Microscopically, the reaction in the liver was observed in its initial stages as an accumulation of leukocytes within the sinusoids. These structures became distended and fibrin threads could be made out lying among the inflammatory cells. This reaction continued until the bordering liver cells were attacked when by extension a fairly well

defined area of necrosis was formed. The alteration occurred in any part of the lobule. At times the areas were quite small and scattered diffusely here and there. They were filled with leukocytes, degenerating liver cells and neuclear debris. Occasionally entire lobules were involved, with the dilated sinusoids packed with leukocytes and the broken liver columns were stained a hemogeneous pinkish red. In several cases definite infarction occurred within the liver directly under the capsule where there was marked infiltration of leukocytes with the formation of small abscesses. Some livers showed an infiltration of lymphocytes in the portal system, while again areas of necrosis frequently bordered closely on these structures. However, the necrosis as a rule began with a crowding of the sinusoids by leukocytes and the reaction then advanced to destruction of liver tissue. In many sections the sinusoids were engorged with blood.

The reactions were noted with both hemolytic and nonhemolytic streptococci, although more frequently with the latter group. However, the reactions with the hemolytic streptococci were at times more intense.

Klotz and Bothwell[42] have called attention to the necrosis found in rabbits treated with streptococci and lesions observed in our animals closely resemble their descriptions.

Lungs.—Seventy-five of the animals showed very congested lungs, many of which presented definite circumscribed hemorrhages scattered over the pleura and throughout the tissue.

Sections of the lungs showed chiefly hemorrhage which was characterized by leakage of blood into the alveoli. This reaction was quite extensive in some places, while again it consisted more of blotchy patches lying close under the pleura. Very often the alveoli were distended with granular, pink-staining lymph either lying free or mixed with desquamated cells. At times the interalveolar capillaries were crowded with leukocytes and even formed small foci with evidence of necrosis. In several sections there was a marked infiltration of leukocytes into the intima of small arteries without involvement of the media. A free media separated the intima from the adventitia, which showed a similar reaction. Some vessels were plugged by thrombi, with invasion of the wall by leukocytes and extension into the surrounding tissue. Several times infarcted-like areas were encountered with the bordering reaction consisting of an admixture of leukocytes, lymphocytes and large endothelial cells.

The reactions observed in the arteries in the lungs are similar to those which have been described by me in the arteries of acute meningitis.

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42. Klotz and Bothwell: Proc. Soc. Exper. Biol. and Med., 1914, **11**, 118.

GENERAL DISCUSSION

From the studies of a number of authors working with different organisms we have learned that the lungs, liver and spleen assume an important rôle in combating all types of infection. It would appear that all animals to a certain degree possess defensive properties against invasion of their blood stream and tissues by infecting agents. This property seems also to be regulated by several factors which influence the course of an infection and the ultimate fate of the host. The virulence of the organisms used, the dosage and the variations in the natural resistance of animals apparently in identical physical condition all contribute to irregularities in the course of experimental infections. We have pointed out elsewhere[43] the marked variations in the character of the infections produced in animals treated with the same organisms under identical experimental conditions. There can be but little doubt that natural immunity varies among animals the same as among human beings. With this fact in view the preciseness of interpretation of experimental bacterial infections must necessarily be limited. Particularly from the work of Bull[44] we have learned that the body is able to care for infection of a certain grade beyond which, however, the animal usually succumbs. This author has found that with the injection into rabbits of a quantity of virulent organisms sufficient to cause death within two to four days the septicemia takes a definite course with slight variations. The bacteria rapidly decrease in number from the time of injection for two to four hours, at which time the blood is sterile or contains only a few bacteria. Within five or six hours the bacteria reappear in the blood and steadily increase until the death of the animal. The initial disappearance of the organisms from the blood is due to the activity of the lungs and liver particularly, and in these locations the organisms are phagocyted following primary agglutination in the blood stream. We have noted in our experiments that these organs do not go unscathed in their effort to rid the blood of the invading organisms, as they quite frequently present areas of necrosis in their structures. Following this protective period the organisms multiply in the blood and vigorously attack the less resistant tissues where they grow and produce focal lesions. In our experiments very large doses of organisms were administered, with the result that the natural barriers of the body were overcome and a wide dissemination of organisms occurred. This widespread infection was attended by the development of focal lesions in many tissues without evidence of selective localization. Even where the

43. McMeans: Am. Jour. Med. Sc., 1916, **151,** 249; idem., The Archives Int. Med., 1917, **19,** 709.

44. Bull: Jour. Exper. Med., 1914, **20,** 237.

same organism was used through several generations and over an extended period of time in rabbits there was little tendency for it regularly to attack a certain tissue. This phase of infection is particularly well illustrated in our work on experimental appendicitis where certain strains of streptococci were studied to determine selective qualities. From this we learned that organisms isolated from joints presented no tendency to localize exclusively in the joints of other intravenously treated animals. The same may be said of organisms isolated from other organs in respect to their source when injected intravenously into rabbits. From this it is difficult to conceive that different strains of the same organism should possess distinct localizing power and should vary consistently in their selective action. Further, the knowledge that we have gained of the mode of blood stream infection does not harmonize with the theory that organs exercise a peculiar avidity for particular organisms. The fate of living bacteria after their introduction into the blood stream of normal animals has been fairly definitely determined. Such organs as the lungs, liver and spleen act in the early stages as the protective barriers of the body. Depending on the dosage and virulence of the organisms used, these barriers may be overcome, and it is then that the less resistant tissues of the body are attacked. We cannot support the opinion that organisms possess a selective quality for organs, which is of a transient nature and disappears after a few days of artificial cultivation. In our work entitled "Experimental Appendicitis" we studied certain strains of streptococci over a period of several weeks and found that these organisms still would attack the appendix in one case after cultivation on blood agar for thirty-eight days with but one animal passage supervening. Another interesting feature which was noted consisted in the marked variation with which the different organs were attacked; even in animals injected with doses from the same subculture, no definite order of invasion was followed. Therefore, organisms which produce an appreciable percentage of lesions in organs other than those from which they are isolated cannot be listed as a particular organ strain.

Regarding the frequency with which the two types of streptococci attacked the several tissues, it was found that there were no marked differences in the percentages of lesions caused by hemolytic and nonhemolytic streptococci in the endocardium, skeletal muscle and periarticular tissues. The green streptococci, however, more frequently produced vegetative endocarditis, while the hemolytic organisms were more commonly associated with subendocardial hemorrhages. In regard to the skeletal muscles, the hemolytic streptococci produced exudative lesions while the green streptococci were found only in connection with

hemorrhages. Lesions in the heart and kidney were more frequently caused by green streptococci, although no great differences were noted between the character of this lesion and that produced by hemolytic streptococci. In the third group of animals the percentage of lesions was in most cases high, due chiefly to the activity of the capsulated gram-negative bacilli. A comparison of the percentages in the three groups of animals presents evidence that there was a general invasion of all the tissues in these animals. There is no evidence to support the theory of selective localization beyond the view that the tissue forms a favorable nidus for the growth of an organism, due either to a peculiar susceptibility on its part or to injury during the "protective period" which precedes a general infection.

Author's Note: This work was carried out under the direction of Dr. John A. Hartwell, to whom I am much indebted for advice and assistance.

PRIMARY ATROPHY OF THE PALLIDAL SYSTEM OF THE CORPUS STRIATUM

A CONTRIBUTION TO THE NATURE AND PATHOLOGY OF PARALYSIS AGITANS *

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INTRODUCTION

The nature of paralysis agitans has been an attractive subject for investigation ever since the publication of Parkinson's[1] celebrated "Essay on the Shaking Palsy" a century ago.

Many strange theories have been advanced and innumerable lesions suggested in explanation of the peculiar phenomena of this interesting disease. But as our knowledge of the pathology and physiology of the nervous system has advanced, many hypotheses, at one time popular, have been discarded and now have only an historical interest. That the subject, however, is still shrouded in uncertainty and mystery, may be readily determined by a perusal of the more recent descriptions in authoritative textbooks of medicine and neurology.

In former years paralysis agitans was described by some authors with the functional diseases, while others believed it to be an affection of the muscular system. It has been held more recently to be related to certain of the ductless glands and especial reference has been made to the parathyroid glands. Many regions of the central nervous system have also had their special vogue and were believed to be the seat of the essential lesion, and it is not so very long ago that pigmentary degeneration of the large motor cells of the spinal cord or of the cerebral cortex was regarded with considerable suspicion in relation to the etiology of the disease.

Much emphasis has also been placed on the evidences of senile and vascular degenerations in the central nervous system of those suffering from this affection and a favorite pathologic theory was the perivascular sclerosis and perivascular gliosis — a not infrequent finding in the white matter of the spinal cord of the older cases — a pathologic condition, however, which is by no means limited to Parkinson's disease.

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* Submitted for publication June 8, 1918.
* Presented at a meeting of the Association of American Physicians, May 3, 1917.

1. Parkinson, James: An Essay on the Shaking Palsy, London, 1817.

PATHOLOGIC CHANGES IN THE BASAL GANGLIA

In recent years, pathologic interest has been chiefly centered in the large basal ganglia, namely, the corpus striatum and the optic thalamus — more especially since the publication of Jelgersma's[2] brief report of the pathologic findings in this disease. Jelgersma noted in a case of paralysis agitans distinct evidences of atrophy in the medullary radiations of the nucleus lentiformis; a reduction in the size of the ansa system—the ansa lenticularis and the ansa peduncularis; together with evidences of atrophy in Forel's field H_1 and H_2; as well as atrophic changes in the nucleus lateralis thalami, the corpus Luysii and the medullary radiations of the substantia reticularis. He emphasized the fact that these atrophic changes in the corpus striatum, the optic thalamus and the hypothalamic region were quite evident and unmistakable.

Jelgersma's pathologic studies were reported only in abstract form, and while very brief and incomplete, they served to direct attention to this region and blazed the trail for much subsequent pathologic investigation.

In the chapter on the "Pathology of Paralysis Agitans," contributed to Lewandowsky's Handbook of Neurology, Lewy[3] in a discussion of these findings, asserts that he has studied serial sections of five cases of paralysis agitans and that an essential atrophy of the ansa lenticularis and of the lenticular radiations does not occur. He modifies this opinion, however, by the statement that some diminution in the number of fibers in the ansa system is of frequent occurrence, and that this is especially well marked in those cases in which there are conspicuous vascular changes in the globus pallidus. In addition, he also notes the existence of atrophic changes in the nucleus basalis of Meynert, the nucleus lateralis of the thalamus and the nucleus paraventricularis thalami.

In a later contribution to the pathologic anatomy of paralysis agitans, Lewy[4] states on the basis of a very extensive histopathologic study of the disease that the essential lesions are localized in the lenticular nucleus, the nucleus of the ansa peduncularis, and the sympathetic vagus nucleus of the medulla; that in typical cases there is a marked increase of the glia elements with degeneration of the ganglion cells, especially of the putamen, less of the globus pallidus, and that many of the ganglion cells show distinct senile fibrillary changes. He

2. Jelgersma: Neu. Anat. Befunde bei Paralysis Agitans und bei chronischen Chorea, Neurol. Centralbl., 1908, **27,** 995.

3. Lewy, F. H.: Paralysis Agitans, Lewandowsky's Handbuch d. Neurol., 1912, **2,** 920.

4. Lewy, F. H.: Zur. Path. Anat. der Paralysis Agitans, Neurol. Centralbl., 1913, **32,** 1305.

closes with the statement that these pathologic changes are essentially senile in character and is at loss to explain the occurrence of the juvenile types of the disease.

Manschot,[5] in an investigation of paralysis agitans, also found a diminution in the number of the ganglion cells and fibers of the optic thalamus, especially of the nucleus lateralis, as well as atrophic changes in the putamen of the lenticular nucleus and in the regio subthalamica.

Quite recently, Auer and McGouch[6] have reported the pathologic findings in two cases of paralysis agitans. In both cases the corpus striatum contained numerous small areas of rarefaction, giving the tissue a somewhat moth-eaten appearance. Many of these spaces contained blood vessels and were quite evidently enlarged perivascular spaces. This *état criblé* was most marked in the lenticular nucleus, but was also present in the optic thalamus, the caudate nucleus, the internal and external capsule and in the corpus subthalamicum of Luys. These observers also noted a reduction of the external medullary layer and the radial fibers of the globus pallidus and in one of the cases there was marked degeneration of cells of the centrum medium of the thalamus and the corpus subthalamicum. They state that the cells of the corpus striatum did not stain well, which may have been due to the age of the material.

It is, therefore, very apparent from this brief review of the more recent literature that certain definite pathologic alterations in the basal ganglia are fairly constant; that vascular and atrophic changes are demonstrable in both the optic thalamus and the corpus striatum, and that no definite concrete conception as to the nature or pathology of the disease has as yet been offered.

ANATOMIC CONSIDERATIONS

The corpus striatum in man is divided by the passage of the internal capsule into two structures, the *caudate* nucleus and the *lenticular* nucleus. The nucleus lentiformis is still further subdivided into an external segment, the *putamen*, and an internal segment, which is termed the *globus pallidus*. These anatomic divisions are purely topographical and are based on the gross appearance of the cells and fiber systems which constitute the ganglion.

Histologically, the putamen is identical in structure with the caudate nucleus, and these two structures constitute the *neostriatum* of comparative anatomy. Both have the same origin and histologic

5. Manschot: Paralysis Agitans, Amsterdam, 1904, F. van Rossen.

6. Auer and McGouch: Pathological Findings in Two Cases of Paralysis Agitans, Jour. Nerv. and Ment. Dis., 1916, **43**, 532.

characteristics, the caudate nucleus being simply split off from the putamen by the passage of capsular fibers.

The globus pallidus is older phylogenetically than the caudate nucleus and putamen (*neostriatum*) and is for this reason sometimes termed the *paleostriatum*. It consists of two segments, an external and an internal, the segmental appearance being produced by the massing of nerve fibers in the lateral and mesial medullary laminae.

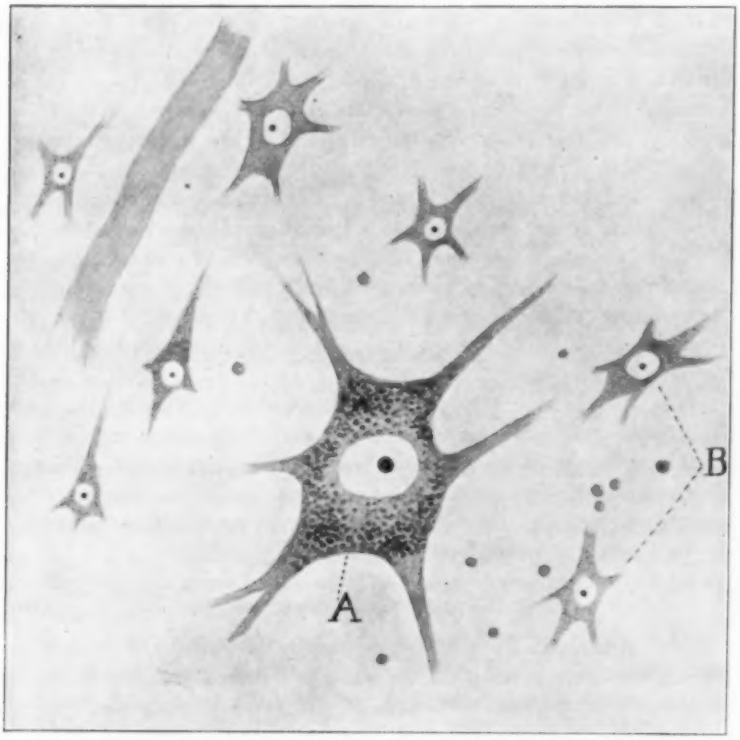

Fig. 1.—Showing normal cell types of the caudate nucleus and putamen (neostriatum). Nissl stain. *A*, large motor cell of globus pallidus type (pallidal cells); *B*, small ganglion cells of the neostriatum (neostriatal cells).

CELL TYPES OF THE CORPUS STRIATUM

From the standpoint of pathologic physiology, a much greater importance is to be attached to the various cellular types of this region than to the mere gross anatomic appearance and subdivisions (Fig. 1).

The neostriatum, that is, the caudate nucleus and putamen, is composed of two separate and distinct types of cells, a *small cell type* and

a *large cell type*. The smaller type of ganglion cell is of pyramidal or polygonal form, and give to the neostriatum a characteristic histologic picture. Scattered among these smaller cells which are very numerous, are ganglion cells of much larger size, of multipolar form, containing a large nucleus, Nissl granules, and quite frequently a deposit of yellow pigment. These *giant cells* of the neostriatum are histologically of the motor type and may be regarded as the homologues in the corpus striatum of the cells of Betz in the rolandic area of the motor cortex.

The globus pallidus (paleostriatum) contains aggregations of ganglion cells which are also of the motor type. These cells are of

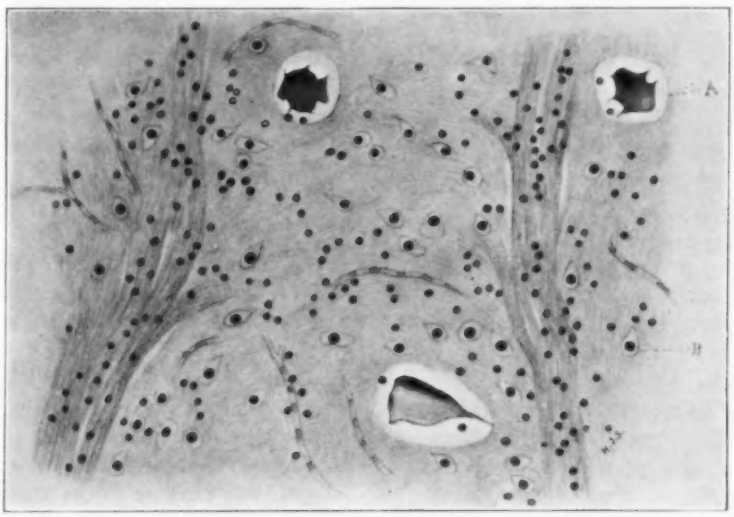

Fig. 2.—The caudate nucleus (hematoxylin-eosin). Juvenile paralysis agitans of twenty-five years' duration. Note atrophy of the large motor cells (A) of globus pallidus type (pallidal cells). The small ganglion cells are well preserved; there is moderate increase of glia cells.

pyramidal and multipolar form, contain a large vesicular nucleus, Nissl granules and frequently clumps of yellow pigment. They are of the same cellular type as are the giant motor cells of the neostriatum and I believe possess a similar function. The corpus striatum is therefore composed of two distinct cellular types, namely, those of the large cell or motor type which is present in both the globus pallidus (paleostriatum) and the caudate nucleus and putamen (neostriatum), and a small cell type which is present only in the neostriatum.

The large motor cells of *globus pallidus type* possess long axis cylinder processes and belong to Type I of Golgi's classification. These

fibers course in the ansa lenticularis and ansa peduncularis terminating in the optic thalamus and hypothalamic region. This motor system I would term the *efferent pallidal system* of the corpus striatum, and the seat of the essential lesion in paralysis agitans.

The small cells of the neostriatum, on the other hand, have short axis cylinders and belong to Type II of Golgi's classification. They terminate in the external and internal segments of the globus pallidus. This is apparently a short association system which unites the caudate nucleus and the putamen to the globus pallidus. It is according to my conception merely an inhibitory and association system for the corpus striatum. This short *neostriatal system* undergoes atrophy in Huntington's chorea and is the essential lesion underlying the choreiform manifestation of this disease (Hunt[7]).

Two fundamental forms of motor disturbances are therefore referable to the cellular systems of the corpus striatum. Atrophy of the small cell or *neostriatal system* is followed by chorea of the Huntington type; while atrophy of the large cell or efferent pallidal system gives rise to the characteristic symptomatology of paralysis agitans.

PRIMARY ATROPHY OF THE PALLIDAL SYSTEM

In a previous monograph,[7] I have considered at some length the functions of the corpus striatum in a discussion of the pathology of juvenile paralysis agitans and its relation to the efferent pallidal system of the corpus striatum.

In the case which formed the basis of this study the disease made its appearance in the fifteenth year, death supervening at the age of 40. The duration of the affection was therefore twenty-five years. Examination of the central nervous system revealed evidences of chronic cellular atrophy with considerable diminution in number of the large motor cells of the corpus striatum. The cellular atrophy was strictly limited to a definite system of cells, namely, those of the motor or globus pallidus type, while the smaller ganglia cells of the corpus striatum were unaffected. I therefore regarded the juvenile paralysis agitans as a motor system disease, the lesion being limited to the efferent projection system of the corpus striatum (Fig. 2).

In addition to the cellular changes there were also evidences of atrophy in the course of the strio-hypothalamic radiations—the ansa system showing definite evidences of thinning The theory was advanced that the corpus striatum contained an important motor system which was termed the *pallidal system*, which through its con-

7. Hunt, J. Ramsay: Progressive Atrophy of the Globus Pallidus (Primary Atrophy of the Pallidal System). A Contribution to the Functions of the Corpus Striatum, Brain, 1917, **40**, 58.

nection with important nuclei in the hypothalamic region, namely, the nucleus ruber, the corpus subthalamicum and the substantia nigra controlled and regulated the extra pyramidal motor system of the spinal cord, namely, the rubrospinal and other descending motor tracts.

THE NATURE OF JUVENILE PARALYSIS AGITANS

The juvenile type of paralysis agitans was therefore regarded as a pure system disease, a neuronal *abiotrophy,* and the suggestion was made that it be distinguished from other types of the Parkinson syndrome as *primary atrophy of the pallidal system.* It was believed to be another evidence of the vulnerability of motor neurons, corresponding in this domain to primary lateral sclerosis and progressive muscular atrophy, as encountered in corticospinal motor neurons.

The opinion was also expressed that Parkinson's disease is not a disease *sui generis,* but a syndrome, and that a variety of pathologic conditions may underly the symptomatology, for example, a primary atrophy or system disease; senile atrophy, vascular and inflammatory lesions, syphilis, tumors, etc.

Evidence was also presented for regarding the corpus striatum and the striospinal system as a mechanism for the control and regulation of automatic and associated movements in contradistinction to the corticospinal system which controls and regulates the higher cortical motor activities, that is, isolated and dissociated movements.

Paralysis agitans was therefore regarded as one of the fundamental types of central palsy characterized by paralysis of automatic and associated movements, rigidity and tremor. It was held that there are two types of central palsy, a *spastic paralysis* characterized by paralysis of isolated and discriminative movements, associated with spasticity of the musculature and referable to lesions of the pyramidal system; and a *paralysis agitans,* distinguished by a paralysis of automatic and associated movements, rigidity and tremor, and referable to lesions of the pallidal system.

In the present study this question receives further consideration and confirmation. In two cases of paralysis agitans of the presenile type characteristic atrophic changes were demonstrable in the large motor cells of the corpus striatum and in the strio-hypothalamic radiations (ansa lenticularis and ansa peduncularis) which I have termed the efferent pallidal system of the corpus striatum.

REPORT OF CASES

CASE 1.—*Summary.*—A man, aged 56, had presented typical symptoms of paralysis agitans for seven years prior to his death. There was general weakness and rigidity; rhythmical tremors of the extremities, face and tongue; the parkinsonian mask and the posture, attitude and gait typical of the disease. Death ensued from infection of the genito-urinary tract and lobular pneumonia.

Histologic Study: The central nervous system showed atrophic changes in the large motor cells of the neostriatum (giant cells of the caudate nucleus and putamen) with slight reduction of the medullary network of the globus pallidus and thinning of the strio-hypothalamic radiation—the ansa system of the corpus striatum.

Clinical Diagnosis: Paralysis agitans.

Pathologic Diagnosis: Primary atrophy of the pallidal system of the corpus striatum.

History.—The patient, aged 53, was for many years a watchmaker. For fifteen years prior to admission he had been employed in the custom house service. He was admitted to the Montefiore Home and Hospital, Sept. 30, 1911, and gave the following account of his illness.

Family History.—This was negative. Both parents were said to have died of old age, the mother suffering in the later years of her life from diabetes and asthmatic seizures. Five brothers were living and in good health.

Personal History.—He had measles and scarlet fever in childhood and typhoid fever in his twenty-seventh year. Eight years ago he developed symptoms of pulmonary tuberculosis with fever, night sweats, cough, loss of weight and hemoptysis. At the end of a year these symptoms abated and he had apparently regained his previous health and strength. He had always been moderate in the use of alcohol and tobacco. With the exception of a mild attack of gonorrhea at the age of 45 he had been free from venereal disease. There was no history of injury. He married at the age of 26, and his wife bore three healthy children. She died six years after marriage during confinement. Subsequently he remarried and had two healthy children. There were no miscarriages in either marriage.

Present Illness.—Three years before admission he experienced a peculiar weakness and stiffness of the right hand which came on gradually and interfered with proper movements of the extremities. This was soon followed by a rhythmical tremor of the hand and fingers. Later a similar tremor made its appearance in the left hand with some tremor of the head. Subsequently his legs became stiff and weak and the gait slow and difficult. There was also a tendency for the walk to develop into a more rapid pace and he was obliged to stop suddenly to avoid pitching forward (propulsion). The condition progressed slowly and was followed two years later by a feeling of general stiffness and rigidity and a constant rhythmical tremor. About this time the articulation also became affected and his speech was tremulous and indistinct.

He complained of no general cerebral symptoms and has been free from headaches and vertigo. His memory is good and sleep is undisturbed. The course of the disease has been slowly and steadily progressive, without pain or parasthesias and consists essentially of weakness and tremor which affects the speech and the movements of the trunk, arms and legs, more especially on the right side. He does not complain of heat sensations or excessive perspiration. There is some drooling of saliva from the mouth at night. Occasionally there is dysuria and at times a purulent discharge from the urethra.

Physical Examination.—This was made in October, 1911. The patient was well nourished and presented no skeletal deformities. He stood stiffly with the head and back somewhat bent. There was considerable stiffness in the movements of the trunk. The face was expressionless and masklike. The musculature was stiff and passive movements showed a waxlike rigidity; the contour of the muscles stood out quite clearly. Nearly all movements were performed slowly and with difficulty. The gait was slow and shuffling, the steps short with a tendency to slouch and drag the legs. When told to walk rapidly the movements became accelerated and propulsion developed. There were evidences of tremor in all four extremities. The arms were more tremulous than the legs and the right side was more affected than the left. The tremor was especially well-marked in the hands and fingers and in the

right hand the posture and the tremor suggested the typical pill rolling movement of paralysis agitans.

The tremor was slow and rhythmical, about three oscillations to the second. The amplitude of the tremor was not very marked and it continued steadily during rest. It varied occasionally in intensity. Usually an active movement of the extremities caused some diminution or even cessation of the tremor. It therefore lacked the quality of an intention tremor. The tremor sometimes increased during action, but always diminished on fixation as when the index finger is applied to the tip of the nose. There was also a slight rhythmical tremor of the lips and tongue. The facial innervation was not so strong on the right side which coincides with the greater involvement of the right arm and leg. The tongue was protruded in the median line and was tremulous. There was some tendency to drooling of saliva. The speech was very slow and drawling. The ocular excursions were normal, and there was no tremor of the ocular muscles. The eyelids were slightly tremulous. The palatal innervation was normal and a laryngologic examination conducted by Dr. Wolf

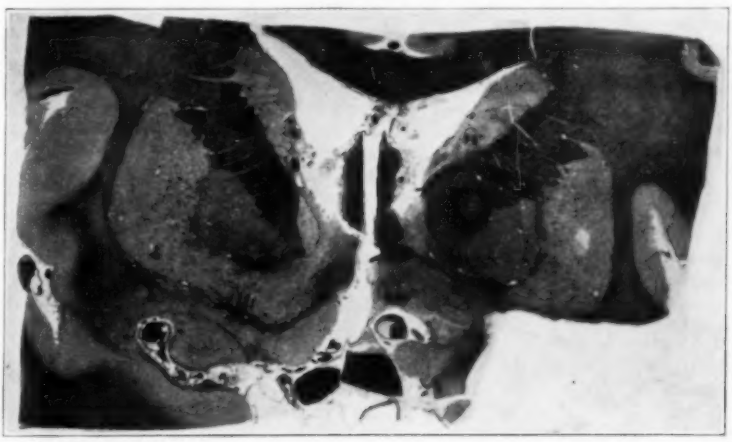

Fig. 3 (Case 1).—Presenile paralysis agitans. Vertical section through the anterior portion of the corpus striatum (Weigert-Pal stain). Note diminution of the fiber network of the globus pallidus proper; the internal capsule is well preserved.

Freudenthal, the consulting laryngologist, showed normal conditions; there was no tremor of the vocal cords. The tendon reflexes of the upper and lower extremities were present and moderately active. There was no ankle clonus and the plantar reflex was of the normal type (no Babinski sign). The pupils were equal and reacted promptly to light and accommodation. The sensations, both superficial and deep, were normal. The outlines of the heart were normal and there were no murmurs. The radial pulses were equal, regular and of good quality. The chest was well developed, symmetrical, with good expansion. Percussion showed some dulness over the left apex. The breath sounds were wheezing and increased over both apices. The prostate gland was hypertrophied and there was residual urine of about 10 ounces.

Note.—The clinical picture presented was typical of paralysis agitans. The patient remained in the Montefiore Home up to the time of his death in May, 1915, his condition gradually growing worse. The Wassermann test of the blood was negative. In November, 1914, he developed dysuria with some

purulent discharge from the urethra. April 1, 1915, a testicular tumor developed on the right side, which was firm and tender and about the size of a small egg. Dr. Hauswirth, who examined the patient at this time, found that the enlargement was confined to the epididymis. The inguinal glands were enlarged on both sides, more so on the right. Systolic blood pressure, 115; diastolic, 85. Later the patient was unable to pass urine and catheterization became necessary.

April 24, 1915, the right side of the scrotum was incised and 2 ounces of pus evacuated. The urine contained albumin, numerous pus and blood cells. Examination of the blood showed a well marked leukocytosis. During the six weeks prior to his death there was irregular fever which reached 106 F. ten days before death.

Report of Necropsy and Pathologic Findings.—The necropsy was performed seventeen hours after death by Dr. A. B. Lambert, pathologist to the Montefiore Home and Hospital. (Necropsy notes made by Dr. Lambert.)

Body: That of a man measuring 158 cm. in length; nutrition fair; rigidity present; postmortem hypostasis over dependent parts; moderate edema of feet and legs; no skin lesions present; no body deformities. In the skin of the scrotum on the right side there is a linear scar about 3 cm. in length to which the testis beneath is adherent. The right testis is considerably enlarged and hard—the left appears to be slightly so. The pupils are moderately contracted. The majority of the upper teeth, especially on the right side are absent, and the remainder poorly preserved. The mucosa of the mouth and eyelids is pale.

Abdomen: There is no exudate in the peritoneal cavity; the peritoneum is everywhere smooth and glistening. The mesenteric lymph nodes are in places slightly enlarged. The liver projects about 2½ cm. below the costal margin in the right mammary line; its lower border shows a tendency to be rounded. The appendix is quite small, is twisted upward behind the cecum, and measures about 5 cm. in length. The diaphragm extends to the fourth rib on the right side and fifth rib on the left side.

Thorax: The thymus is replaced largely by fat; both pleural cavities are free from fluid; both lungs are free except in the region of their apices, where they are tightly bound by old adhesions. The pericardial cavity contains a slight excess of clear fluid; the pericardial surface is smooth and shiny. There is a slight excess of epicardial fat.

Heart: The heart weighs 350 gm.; the right auricle contains only a postmortem clot. The epicardium is everywhere smooth and shiny; the tricuspid opening admits the tips of three fingers, and measures in circumference about 11½ cm. The cusps are quite delicate. The right ventricular wall measures 3 to 5 mm. Over the apex the muscle is replaced in considerable part by fat. The musculature is rather pale. The pulmonary opening measures about 7 cm. The cusps are quite delicate. The left auricle is normal. The mitral valve easily admits the tips of two fingers and measures about 11 cm. in circumference; its cusps are not thickened, although near the area of attachment there are a few yellow opacities which are distinctly seen on the ventricular surface. The left ventricle appears to be slightly dilated, its wall measures about 1 cm. in thickness. The musculature in places has a distinctly grayish yellow cast, and the fibers look a little coarse. The aortic opening measures 8 cm. in circumference; its cusps are practically normal, as is also the first portion of the aorta. The coronary vessels are practically free from atheroma.

Lungs: The right lung weighs 600 gm. The periphery is everywhere smooth and free from exudate, except the apex, where there are some old fibrous tags, and there are numerous depressed scarred areas, which on palpation are firm and nodular. The greater part of the upper and middle lobe is air containing, and moderately collapsed. The lower lobe is much more voluminous, and its lower and posterior parts, while crepitant, are somewhat "meaty" on palpation. Section through the upper lobe shows in region of the depressed areas many irregular, pigmented fibrous areas, and in addi-

tion a number of small gray nodules—evidently tubercles. Section through the remainder of the upper lobe and the median lobe shows dry, relatively nonpigmented air-containing lung tissue. The lower lobe, however, presents on section a bright red color. Some fluid and considerable blood exudes from the cut surfaces. There are some areas indefinitely outlined somewhat darker than the rest which suggest pneumonic consolidation, but they are not sharply circumscribed. The left lung weighs 450 gm. Superficially it is similar to the right. There are the same old tuberculous lesions in the apex. The lower lobe posteriorly is likewise heavy, filled with blood and a few distinct patches of lobular pneumonia can be made out.

Liver: The liver weighs 1,875 gm. Both lobes of the liver are decidedly enlarged. The lower surface is distinctly rounded, especially the left lobe. The surface is smooth. The color is finely mottled; just beneath the capsule in the upper part of the right lobe there is seen a grayish yellow nodule which on section measures about 2 mm. in diameter, evidently a calcifying thrombus in superficial vein. On cut section the lobulation is fairly distinct, the lobes

Fig. 4 (Case 1).—Vertical section through the middle of corpus striatum, showing thinning of the ansa lenticularis and diminution of fiber network of the external segment of the globus pallidus.

are of uniform size with reddish centers and slightly paler periphery. The gallbladder is filled with bile, its wall is thin; it contains no stones.

Spleen: The spleen weighs 220 gm. It contains two deep notches on its upper border; it is firm; its capsule is not thickened. On section the lymphoid tissue is abundant and rather prominent. The trabeculae are not thickened.

Kidneys: The right kidney weighs 150 gm. and is of about normal size, measuring about 11 by 6 by 2½ cm. On removing the capsule a smooth surface is disclosed in which the vessels are decidedly injected. On section the cortex is seen to measure about 7 mm. The glomeruli are easily visible, the markings are regular. In one of the pyramids a small grayish yellow focus is seen, about 2 mm. in diameter—evidently an abscess. The pelvis is dilated, its mucosa is thickened, the vessels decidedly injected, and occasional hemorrhages are seen. The ureter cusp in its lower portion shows less marked evidence of inflammation. The left kidney weighs 200 gm. and is much enlarged; its capsule is easily removed. The surface is of a deep red hue. On section a quantity of blood exudes from the cut surfaces; the cortex mea-

sures about 8 mm. in thickness; the markings are normal. Occasional gray yellow foci are seen in the pyramids. The pelvis is somewhat dilated. The ureter is dilated, and its mucosa presents the same appearance as that of the pelvis of the kidney.

Bladder: The tissues around the bladder are extremely edematous; the bladder itself is distended with very foul, purulent urine; its wall is greatly thickened, measuring 1.5 cm. in most places. The crests of the mucosa are of a reddish black color, showing in places grayish exudate. In general, however, there appear to be no ulcerations. The vessels are all greatly injected. There are a number of small crypts and diverticula present in all parts of the bladder. Between the folds of the mucosa the inflammatory condition is less marked, the mucosa being edematous but not particularly injected, and showing no definite exudate.

Prostate: The prostate is enormously enlarged, measuring roughly 3½ cm. anteroposterior diameter. The enlargement is uniform. No definite abscesses are seen, but from the seminal vessels a purulent fluid can be expressed. The right testis, except for some increase in consistence, appears normal. The right epididymis, however, is greatly indurated, and shows a number of purulent foci. The wall of the vas deferens is considerably thickened. The left testis and epididymis are similar to the right, though the changes in the epididymis are less marked.

The esophagus is normal. The stomach shows postmortem digestion. The intestines, pancreas, larynx, trachea and thyroid are normal.

Parathyroids: These were removed for microscopic study.

Aorta: Shows a few early atheromatous changes throughout its entire extent. The iliacs show a striking longitudinal wrinkling.

Brain: The brain weighs 1,260 gm. The skull is normal; the meninges are normal; slight edema of the pia arachnoid. There is a marked arteriosclerosis of the basilar vessels of the circle of Willis. The brain and cord were placed in formalin and preserved for microscopic study.

Histologic Study of the Glands and Viscera.—(Dr. Lambert.) Heart: In places the muscle fibers are quite large. There are occasional small scars.

Lungs: Section 1.—There are patches of confluent lobular pneumonia. In the exudate there are many red blood vessels and much pink staining coagulated fluid. The bronchi are filled with pus. Section 2.—This includes a large nodule made up of old pigmented scarred tissue in which a number of fresh tubercles are seen and occasional lymphoid nodules. The tubercles all show large giant cells; in at least one of the giant cells there is one of the curious star-shaped glassy structures such as have been described by Wolbach, Wood and others (Proc. New York Path. Soc., May, 1915).

Kidneys: The parenchyma is practically normal. The pelvic fat is increased in amount. The submucosa of the pelvis is thickened and infiltrated with leukocytes, and contains nests of epithelium, probably representing new growths from the mucosa (crystitis cystica?). No exudate on the surface is seen.

Liver: The cells around the efferent vein contain a considerable quantity of yellowish-brown pigment. There is a slight increase of connective tissue about the portal vessels.

Bladder: There is a marked hypertrophied muscular element. The mucosa is much thickened. Its epithelial covering is gone, leaving a very vascular hemorrhagic ulcerated surface. There is a great infiltration of the mucosa by wandering cells of all types.

Ureter: The wall seems thickened, but there is no evidence of an acute inflammatory reaction.

Seminal Vesicles: The connective tissue and nuclear elements are greatly increased. There is a slight infiltration by wandering cells, especially eosinophils. There is a marked papillary growth from the mucosa of the ducts. The papillae and polypoid masses are composed of cellular connective tissue and are covered by cuboidal or flattened epithelium.

Vas Deferens: The wall is enormously thickened, and shows chronic inflammatory changes.

Prostate: The parenchyma is rather abundant. Many of the follicles are dilated and contain a lot of necrotic epithelium and pink staining fibrinous material. Other glands show a papillary hyperplasia of the lining cells. There is very little in the way of inflammatory reaction.

Testis and Epididymis: There is a great increase of connective tissue stroma of the epididymis. There is also a diffuse fibrosis of the testis, and the tubules are small and atrophic looking—resembling more those of the kidney than normal testis. The larger blood vessels show thickened walls.

Hypophysis: The glandular portion is normal. The pars nervosa contains a number of pigment containing cells. The pigment is in the form of small uniform hyaline granules.

Skeletal Muscles: (Biceps.) The muscle fibers are small, and the sarconuclei increased in number. Occasional encysted trichinae are seen. The capsule is a pink staining, hyaline, laminating material. In the parasites fine particles of lime are deposited.

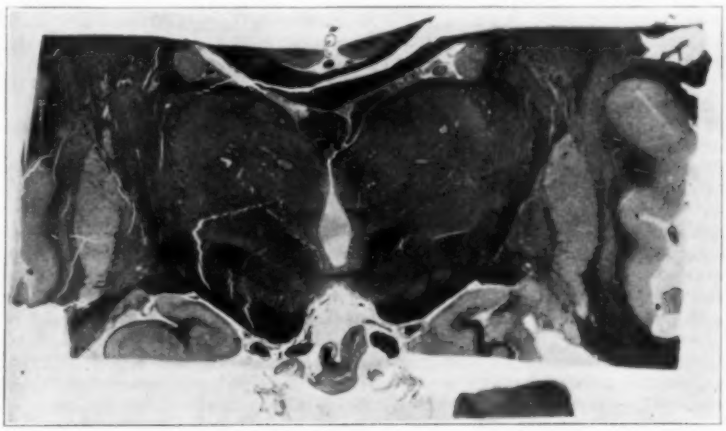

Fig. 5 (Case 1).—Vertical section through the optic thalamus and corpus Luysii, showing thinning of the strio-hypothalamic radiations.

Thymus: The thymus is made up chiefly of connective tissue and fat separating islands of thymic tissue. In these islands there are occasional small cysts containing necrotic pink staining material.

The parathyroids revealed no pathologic changes.

Microscopic Examination of the Central Nervous System.—Sections were made from the cerebral cortex, the cerebellum, pons, medulla oblongata and spinal cord. The basal ganglia were cut in serial section and stained with toluidin blue, hematoxylin-eosin and by the Weigert-Pal method.

Spinal Cord: Sections of the cord show no essential changes. The anterior horn cells are well formed, presenting a normal tigroid appearance, a well formed nucleus and nucleolus and well developed processes. There are no pathologic alterations of the Nissl granules, and no excess of pigment. Rarely a somewhat shrunken cell is observed, but these are quite isolated and infrequent.

There is no thickening of the meninges and the blood vessels are free from thrombi or noteworthy arteriosclerotic changes. There is no perivascular sclerosis, or gliosis. There is a considerable deposit of corpora amylacea in the

region of the posterior columns and posterior horns. Weigert-Pal sections show no evidences of tract degeneration. There are no signs of sclerosis in the areas occupied by the direct and crossed pyramidal tracts.

Medulla: The nuclei and nerve tracts are normal in appearance, and show no signs of degeneration or atrophy.

The pons varolii is also normal. The fillet, pyramidal tracts, the posterior longitudinal fasiculus and peduncles are normal.

Cerebellum: Sections of the cerebellar cortex including the dentate nucleus are normal. The cellular layers of the cerebellar cortex including the large cells of Purkinje are well preserved and of normal appearance.

Cerebral Cortex: Sections from the frontal, rolandic and occipital areas show no essential lesions. The cellular layers and medullary radiations present a normal appearance and especially noteworthy is the preservation of the large pyramidal cells of the motor area. The cells of Betz are preserved and show no evidences of atrophy. Occasional atrophic cells are noted in the cortex, more especially in the frontal region, but these are isolated and comparatively infrequent. The meninges are normal and the blood vessels show moderate thickening of their walls.

The basal ganglia were sectioned in serial slices, some of these were cut in thin sections (10 microns) and stained by various cellular methods, the remainder were treated by the Weigert-Pal method. This permitted a fairly complete survey of the various structures and levels of the corpus striatum and of the optic thalamus for both cellular changes and tract degeneration. (The serial sections of the basal ganglia were prepared in the New York Psychiatric Institute under the direction of Dr. Charles B. Dunlap.)

Caudate Nucleus and Putamen: The large ganglion cells of the globus pallidus type (giant cells) which are scattered through the neostriatum show well marked atrophic changes in the head, body and tail of the caudate nucleus and the putamen. They are apparently not reduced in number. Generally speaking, these atrophic changes are more marked in the anterior portions of the striatum. The giant cells are considerably shrunken and reduced in size; the nucleus is absent or displaced laterally, very much contracted, presenting a shrunken, shrivelled appearance. The processes of the cells are often fragmented or atrophic and of cork-screw or twisted configuration. Many of the cells contain an excess of coarse yellow pigment granules, and not infrequently the pericellular and perivascular spaces in this region are observed to contain detritus consisting of granules of a yellowish lipoid material.

The small ganglion cells of the caudate nucleus and putamen are normal in number and appearance and the evidences of cellular atrophy are therefore limited to the large motor cells of the globus pallidus type, namely, the giant cells of the neostriatum. There is no distinct increase of glia elements, although the pericellular spaces of atrophic cells sometimes contain small groups of parasite glia nuclei.

The atrophy of the ganglion cells in the caudate nucleus and putamen is therefore a selective one, limited to a single and definite cellular type, namely, those of so-called *globus pallidus type*. These cells have the structure and appearance of motor cells and are not unlike those of the rolandic area of the cerebral cortex and the anterior horns of the spinal cord.

Globus Pallidus: The ganglion cells of the globus pallidus proper (paleostriatum) are not reduced in number and are not definitely atrophic; many however, appear reduced in size and present a rounded or somewhat angular appearance. The nucleus and nucleolus are preserved but frequently appear smaller than normal; and the Nissl granules are often absent or not sharply defined, the protoplasm appearing homogeneous and of a somewhat hyaline appearance. Many of these cells contain a considerable amount of yellow pigment.

The blood vessels of the corpus striatum and especially of the globus pallidus show some arteriosclerotic changes with thickening of the vessel walls,

more particularly of the media. There are no thrombotic occlusions, and no areas of softening or hemorrhage are noted. Many of the perivascular spaces contained clumps of yellowish and dark granular pigment and in the globus pallidus these are somewhat dilated. The dilatation of the perivascular spaces in the more anterior portions of the globus pallidus producing a slightly cribriform appearance (*état criblé*).

The ganglion cells of the *corpus Luysii, nucleus ruber,* and the *substantia nigri* appear normal in the specimens examined, except for an occasional isolated atrophic cell.

The optic thalamus shows no evidences of cellular changes or atrophy except for an occasional atrophic cell which stands out sharply from the normal cell groups. The cells of the *nucleus internus, nucleus medialis, nucleus lateralis* and the *nucleus anterius* are normal in appearance and number.

The blood vessels of the thalamic region show arteriosclerotic changes with thickening of the vessel walls and occasionally a dilated perivascular space. There are, however, no evidences of thrombosis, hemorrhage or softening.

Basal Ganglia (Weigert-Pal method): [Figs. 3, 4 and 5.] The general topography and medullary markings of the corpus striatum are well-preserved. There are no evidences of gross vascular lesions. The small pencil-like medullary bundles of the caudate nucleus and putamen are normal in size and appearance, as they traverse the neostriatum and may be traced into the globus pallidus.

The medullary network of the globus pallidus proper appears to have undergone a slight fiber reduction so far as it is possible to judge by this method. The reduction in the medullary network is more apparent in the anterior portion of the globus pallidus and involves especially its external segment, the external medullary lamina and the supplementary external lamina. The internal medullary layer appears to have undergone only slight if any reduction in its fiber content. The ansa lenticularis in its more anterior portion also shows some thinning of its fiber content and this atrophy appears to be more evident on one side than on the other. More posteriorly the ansa peduncularis appears to have undergone only very slight atrophy, which is also true of Forel's lenticular bundle (H_2) and the strioluysian fibers.

Forel's commissure and Meynert's commissure of the hypothalamic region are both present and have apparently suffered no reduction in their fiber content. Forel's thalmic field (H_1) is also normal and the medullary capsule of the red nucleus is apparently not reduced in size. The corpus Luysii shows no evident diminution of its fiber content and only slight if any reduction of its medullary capsule. The internal capsule and the pes pedunculi are normal. There are no evidences of atrophy in the pyramidal tracts of the crus cerubri or of the brachium conjunctivum. In the fasciculus longitudinalis posticus and the tegmental region there is no obvious loss of nerve fibers.

The external and internal medullary layers and the *zone grillagée* of the optic thalamus are normal, and there is no evident reduction of the striothalamic radiations.

The only demonstrable pathologic changes were the atrophy of the large ganglion cells of the caudate nucleus and putamen (the neostriatum) and a corresponding diminution of the fiber network of the globus pallidus and of the striohypothalamic radiations.

Case 2.—*Summary.*—A man, aged 52, presenting the typical clinical picture of paralysis agitans of ten years' duration. There was general rigidity and tremors of the paralysis agitans type; a parkinsonian mask, almost complete dysarthria, and the gait and attitude typical of this disease. Death from bronchopneumonia.

Histologic Examination: Central nervous system revealed atrophic changes in the large motor cells of the corpus striatum, namely, the caudate nucleus and putamen. Many of the giant cells of the neostriatum were in various stages of chronic cellular atrophy. In addition there was some loss of the

medullary network of the globus pallidus and a thinning of the striohypothalamic radiation, namely, the fibers of the ansa system.

Clinical Diagnosis: Presenile type of paralysis agitans.

Pathologic Diagnosis: Primary atrophy of the pallidal system of the corpus striatum.

History.—The patient, aged 52, was a manufacturer of dress trimmings. He was admitted to the Montefiore Home and Hospital Nov. 4, 1914. Owing to the speech disturbance much of the history was obtained from his mother.

Family History.—His father died of cancer, aged 67. His mother, aged 68, is in good health. There is no history of any familial disease. The patient is the oldest of six children and emigrated to this country twenty years ago. He married but was divorced and had no children. No history of venereal disease was obtained. He had been engaged for many years in the manufacture of dress trimmings and was moderate in the use of alcohol and tobacco.

Present Illness.—The malady from which he now suffers made its appearance ten years before admission to the hospital and began with weakness of the arms and hands. He was soon forced to give up work and remained at home, the arms gradually growing weaker. Subsequently a rhythmical tremor developed which has continued ever since, gradually increasing in extent and severity. Later the legs became affected and for the past four years the gait has shown considerable impairment. There also developed a curious tendency to acceleration of the step in walking (propulsion) from which he suffers at the present time. For the past three years the speech has shown distinct impairment and there is now considerable difficulty in forming words. There is a constant tendency to drooling of saliva and some difficulty in deglutition. All movements are labored and difficult and with the tremor and marked dysarthria a state of considerable helplessness has resulted. During his long illness there has been no history of general cerebral symptoms such as headache, vertigo, or apoplectiform attacks, and the whole progress of the disease has been slowly and insiduously progressive.

Physical Examination.—The patient walks slowly and with great difficulty, owing to the general rigidity of the musculature. A well marked tendency to propulsion is present. The attitude and gait are typical of paralysis agitans. Both the arms and legs are rigid on passive movement and there is well marked rigidity of the abdominal musculature. The contour of the muscles is very well defined and the musculature presents a waxlike firmness on direct pressure. The tendon reflexes of the upper and lower extremities are present and are not exaggerated. The plantar reflexes are normal. The abdominal and cremasteric reflexes are present and equal on the two sides. The pupils are equal and react to light and accommodation. There is no nystagmus or tremor of the ocular muscles. Sensation is quite normal. The mentality so far as could be determined was not affected. The outlines of the heart are normal and there are no murmurs. The radial pulse is regular—84 beats to the minute and equal on the two sides. Systolic blood pressure, 120. The lungs are normal to percussion but auscultation is unsatisfactory owing to the poor expansion of the chest. So far as could be determined the breath sounds are normal. Urine: acid; specific gravity, 1.030; no albumin and no sugar.

Note.—The patient remained in the neurologic wards of the Montefiore Home in practically the same condition until April 9, 1915, when symptoms of pneumonia developed. His breathing became rapid and labored; temperature rose to 104.6 F., pulse 110. Dulness on percussion was noted over the right lower lobe, with bronchovesicular breathing anteriorly and diminished sounds posteriorly. April 11, 1915, his condition was much worse and he became stuporous, with stertorous breathing. Examination of the cerebrospinal fluid was negative. The Wassermann test was negative. Death occurred April 12, 1915.

Report of Necropsy and Pathologic Findings.—(Necropsy notes made by Dr. A. B. Lambert.) Body: That of a moderately emaciated man, 158 cm. in length. There is a distinct curvature of the back, with drooping forward of the shoulders. There are no skin lesions.

Abdomen: There is no fluid. The intestines are freely movable. The appendix extends into the pelvis, and measures about 6 cm. in length. The mesenteric glands are not enlarged. The liver projects about 3 cm. below the costal margin. The thymus is atrophic. Both lungs are free anteriorly. The right is densely adherent to the diaphragm about the base. The pericardium contains about 30 c.c. of clear fluid.

Heart: It weighs 260 gm. It is distended with blood, especially on the right side. The pericardium is everywhere smooth. The precordial auricle is normal. The tricuspid opening admits three fingers, and measures in circumference about 11 cm. There is a slight thickening, especially of one of the cusps. The right ventricular wall measures about 4 mm. in thickness. The pulmonary valve is normal and measures about 7 mm. in circumference. The

Fig. 6 (Case 2).—Presenile paralysis agitans. Vertical section through anterior portion of corpus striatum (Weigert-Pal stain). Note diminution of the fiber network of the globus pallidus proper; the internal capsule is well preserved.

left auricle is normal. The cusps of the mitral valve are moderately thickened, especially near their margin, but no fresh vegetations are seen. The left ventricular wall measures about 1.3 mm. in thickness. The aortic valve measures 8 cm. in circumference—its cusps are practically normal. The aorta is quite elastic, and shows only very early atheromatous changes.

Lungs: The right lung is very voluminous, and weighs 1,100 gm. Anteriorly is air-containing, but posteriorly is firm and nodular. The pleura presents a mottled black and gray color, from the enormous amount of coal pigment present. On section through the firm consolidated portion there is seen a patchy consolidation, the consolidated parts being lighter in color and slightly elevated above the surface. From the bronchi there exudes thick, creamy pus. In the lower lobe there is an area to which the diaphragm is firmly attached, and which shows on section an irregular cavity about 2½ cm. in length which connects with the small bronchus. A necrotic, purulent but not very foul material fills this cavity. The larger bronchi are filled with pus.

The glands about the hilum are deeply pigmented, very firm and in some places suggest calcification.

The left lung is similar to the right, weighs 800 gm. The glands at the hilum are quite firm, pigmented, and there is one which on section shows grayish yellow, suggesting tubercle.

Liver: Weighs 1,400 gm. It presents a normal shape, except for a perpendicular depression over the right lobe. At one point on the surface is seen a small number of yellow nodules which project slightly, and which on section are distinctly caseous. The nodules measure about 0.5 mm. in diameter and extend for a similar distance into the lobe. On cut section the liver is grayish red in color—the lobulation is fairly distinct. The gallbladder is unusually long, and contains no stones.

Spleen: Weighs 150 gm. Is normal in shape. It is quite firm on section. The trabeculae are prominent. In the capsulae are seen a number of tiny gray nodules, less than 1 mm. each in diameter—they do not extend into the substance of the spleen. The malpighian bodies are not very distinct.

Kidneys: These organs together weigh 300 gm. and are alike. The capsules strip easily. The cortex measures from about 6 to 7 mm. The glomeruli are quite prominent. There is a fair amount of pelvic fat. The pelvis and ureters are not dilated.

Bladder and Prostate: These are normal.

Pancreas and Stomach: These show the usual postmortem changes.

Larynx, Trachea and Thyroid: Normal.

Brain: There is a definite edema of meninges of the upper convexity. The sulci are quite wide and deep, suggesting some atrophy; especially in the frontal portion of the cerebrum. Section through formalin hardened specimen shows no gross lesion. The cortex does not appear to be definitely reduced in thickness. The vessels of the circle of Willis show some arteriosclerotic plaques but no evidence of thrombosis. The cord presents normal architecture and appearance. The brain and spinal cord were preserved in formalin for histologic examination.

Microscopic Examination of the Glands and Viscera.—(Made by Dr. Lambert.) Heart: The muscle fibers are rather small. They contain, however, very little pigment. There is a slight increase in connective tissue about the blood vessel.

Lung: Section 1.—There is a confluent lobular pneumonia in the lower areas; polynuclear leukocytes predominate in the exudate, about the borders of such areas the alveoli contain many large mononuclear cells and a considerable quantity of coagulated fluid. In some of the alveoli are bluish masses suggesting bacteria. The bronchi are filled with pus cells.

Section 2 (through the cavity near base of right lung).—There is on one side a necrotic surface; in this is seen a vascular granulation tissue which merges gradually into the adjacent lung tissue. The lung alveoli are all collapsed. There is a great increase in the thickness of the septa. The pleura is also greatly thickened. The fibrosis suggests a chronic lesion—probably a bronchiectatic cavity. This cavity may have served as the starting point of the extensive lobular pneumonia. The blood vessel walls are rather thick, the sinuses are filled with blood. The trabeculae are of normal size.

Liver: The section includes one of the caseous foci observed beneath the capsule—the connective tissue capsule surrounding this caseous material is undoubtedly an old thrombus mass. There appears to be little tendency toward oragnization. The liver itself presents the picture of a moderate chronic passive congestion. The capillaries are dilated, but there is no necrosis of liver cells.

Kidneys: The organs show no marked alteration.

Prostate: The follicles are rather large and abundant.

Thyroid: The follicles are not very large, but contain abundant colloid, which stains well.

Parathyroids: There is some increase in connective tissue about the larger blood vessels. The cells appear normal.

Arm and Neck Muscles: Appear normal.

Muscle of Back: The muscle of back stains very poorly—changes seen are probably postmortem.

Histologic Examination of the Central Nervous System.—The brain and spinal cord were preserved in formalin and studies were made of the cerebral cortex, the cerebellum, medulla oblongata, pons varolii, spinal cord, the corpus striatum, optic thalamus and subthalamic region. The following stains were used: Toluidin blue (Nissl), hematoxylin-eosin, Sim's stain, and the Weigert-Pal method. Serial sections from the region of the basal ganglions were prepared in the New York Psychiatric Institute under the direction of Dr. Charles B. Dunlap. The basal ganglions were cut in vertical slices some of which were stained for cellular studies and the remainder cut in serial sections and stained by the Weigert-Pal method.

Spinal Cord: The anterior horn cells are normal in appearance and in number. The nucleus is large and well formed, the nucleolus stands out clearly

Fig. 7 (Case 2).—Vertical section through middle of corpus striatum showing thinning of the ansa lenticularis and diminution of fiber network of the external segment of the globus pallidus.

and the normal tigroid appearance of the Nissl granules is well defined. There is no excess of pigment. The meninges and blood vessels show no noteworthy alteration. There is some thickening of the media in certain of the vessels, but no evidences of thrombosis or of hemorrhage. There are numerous corpora amylacea scattered throughout the section, especially in the region of the substantia gelatinosa of the posterior horns. There are no signs of perivascular gliosis or sclerosis. Weigert-Pal studies show no evidences of tract degeneration and the regions occupied by the direct and crossed pyramidal tracts show no sclerosis. Sections of the medulla oblongata are normal. The pyramids, the lemniscus and other tracts of the medulla are well formed and show no signs of atrophy. The nuclei of this region are normal. The pons varolii is normal.

Cerebral Cortex: Sections were made of the frontal, occipital and rolandic areas. The cyto architecture was normal, and there was no extensive evidence of cellular atrophy or degeneration. Here and there atrophic ganglion cells, intensely stained, were noticeable, but such cells were few in number and widely

separated. The cells of Betz in the precentral convolution were well formed and free from atrophic changes. The medullary rays and markings of the cortex by Weigert's method were of fairly normal appearance and showed no especial diminution. The cerebellar cortex and dentate nuclei are normal. The Cells of Purkinje are well formed and of normal appearance.

Optic Thalamus: Sections through the anterior, middle and posterior portions of the optic thalami show no essential lesions. The cells of the nucleus anterius, nucleus lateralis and medialis are not diminished in number and show no evidences of atrophy. The medullary laminae of the thalamus are well preserved, as are Forel's thalamic bundle H_1 and the medullary capsule of the nucleus ruber. The cells of the corpus Luysii are well preserved and free from atrophic changes.

Corpus Striatum: The caudate and the lenticular nuclei are free from any evidences of gross lesions. The blood vessel walls are thickened, especially the middle coats, but the lumen is free and there are no thrombi. In the globus pallidus the perivascular spaces are rather large and there is a slight cribriform appearance as a result of these vascular and perivascular changes. Many of the perivascular spaces contain clumps of yellow and dark brown pigment (lipoid material) and such pigment granules are also encountered in some of the perivascular spaces.

Ganglion Cells of the Corpus Striatum: The small cells of the caudate nucleus and of the putamen are normal in number and appearance. In contrast to these, the large motor cells of the globus pallidus type in the caudate nucleus and putamen show definite signs of atrophy. These changes are especially well marked in the more anterior portion of the ganglia. The atrophic changes in the large multipolar cells of the neostriatum (giant cells) consist of shrinkage and atrophy of the cell body; thin and atrophic processes; a small, irregular and displaced uncleus staining a uniform and intense blue with hematoxylin. In some cells the atrophy and shrinkage are so marked as to prevent the differentiation of nuclear structure. Such cells are often shrunken and of a hyaline appearance. In many of the cells the protoplasm is broken up into coarse granules of a yellowish tinge and appear to have undergone pigmentary degeneration. Many of the atrophic cells are surrounded by groups of parasite glia cells, lying in the pericellular spaces. These changes, which are quite general and well marked in the more anterior portions of the corpus striatum, are less prominent more posteriorly.

Globus Pallidus: The large multipolar cells of the globus pallidus type are well preserved and are not diminished in number. Many of these cells, however, are somewhat reduced in size and present a more rounded or angular appearance than usual. Many of the cells are filled with coarse, light yellow pigment granules. The nucleus and nucleolus are well preserved. The fiber systems of the corpus striatum by the Weigert-Pal method show slight but distinct evidences of atrophic changes. The small pencil-like medullary bundles which pass from the caudate nucleus and the putamen into the globus pallidus are well preserved and have undergone no reduction in size or number. The external medullary lamina and the supplementary external lamina of the globus pallidus appear distinctly thinner than normal, and the external segment of the globus pallidus shows a distinct reduction in its network of medullated nerve fibers (Figs. 6, 7 and 8). In the anterior portions of the globus pallidus the diminution of the fiber network is quite marked. The ansa lenticularis and ansa peduncularis are fairly well preserved but especially in the more forward portion of the ansa system appear thinned and atrophic. A slight thinning of Forel's field H_2 and of the strio-luysian fibers is also present. Meynert's commissure and Forel's commissure are present and apparently have undergone no diminution in size. The essential pathologic changes were an atrophy of the large ganglion cells of the caudate nucleus and putamen (neostriatum) and a corresponding diminution of the fiber network of the globus pallidus and of the strio-hypothalamic radiations or ansa system.

COMMENTS ON THE PATHOLOGIC STUDIES OF CASES 1 AND 2

The cases just recorded are typical examples of the presenile type of paralysis agitans. In Case 1 the duration of the disease was about seven years and in Case 2 approximately ten years; both died of acute intercurrent affections. All of the cardinal symptoms of the disease, namely, paralysis, rigidity and tremor were present and quite generalized.

In the examination of the central nervous system, especial attention was given to the basal ganglia. In these structures there were no evidences of gross lesions, such as hemorrhage, softening or inflammation. The blood vessels were somewhat thickened, especially in the

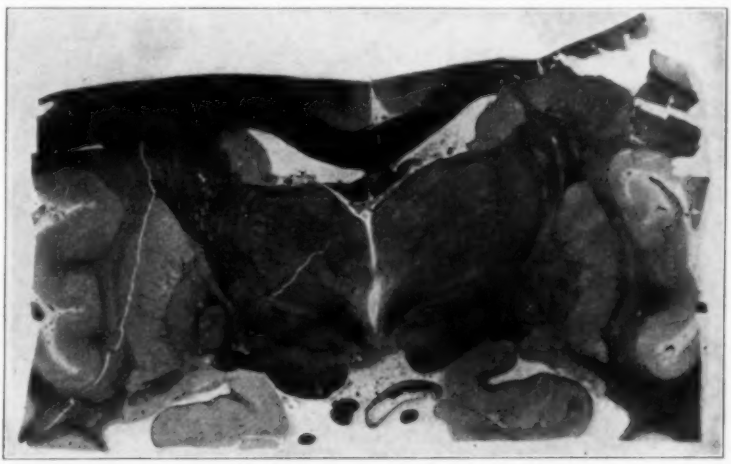

Fig. 8 (Case 2).—Vertical section through the optic thalamus and corpus Luysii, showing thinning of the strio-hypothalamic radiations.

region of the globus pallidus, where a slight appearance of *état criblé* was produced. There were, however, no evidences of thrombosis.

The most striking pathologic changes noted were in the large motor cells of the caudate nucleus and putamen. Many of these giant pallidal cells of the neostriatum were in various stages of chronic cellular atrophy (Fig. 9). The cells were reduced in size, the bodies shrunken, atrophic and shivelled processes, with an elongated contracted nucleus, occupying a lateral position in the cell body. Pyknosis of the nucleus was a very striking feature in many cells, while in others the entire cell was much shrunken and diffusely stained. Many cells showed evidences of advanced pigmentary degeneration and many of the perivascular and pericellular spaces of the corpus striatum contained pig-

ment detritus and yellowish lipoid material. The large cells of the striatum did not appear to be reduced in number, but were simply in various stages of chronic atrophy; there was no noteworthy increase of the glia cells in this region.

In contrast to the atrophic changes in the giant pallidal cells of the neostriatum, the small ganglion cells of this region (neostriatal cells) were preserved, both in number and appearance, and were free from evidences of atrophy (Fig. 9). The cellular changes were more pro-

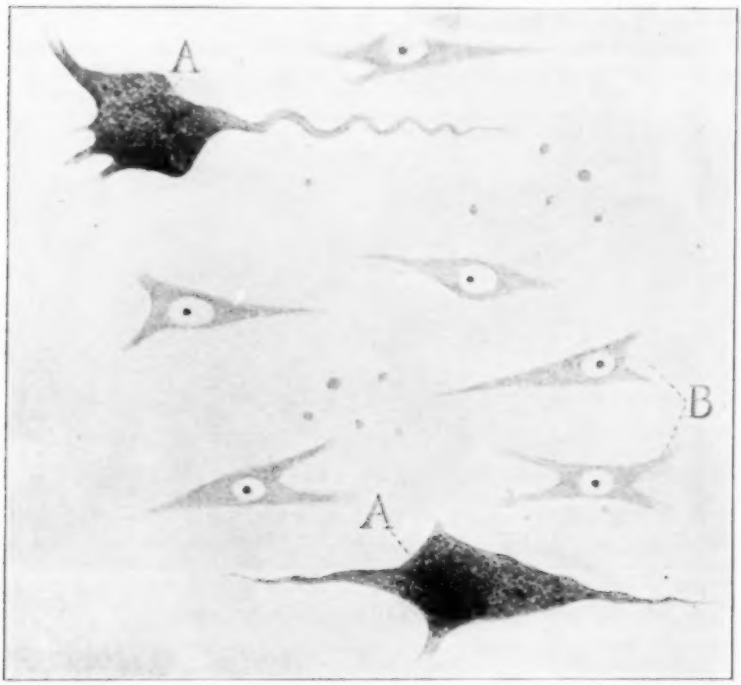

Fig. 9.—Showing atrophic ganglion cells of the caudate nucleus and putamen (neostriatum). Nissl stain. Presenile paralysis agitans of ten years' duration. *A*, atrophy of large motor cells of the pallidal type; *B*, small ganglion cells are normal.

nounced in the anterior portion of the corpus striatum, although occasional atrophic cells of the large globus pallidus type were demonstrable as far posteriorly as the tail of the caudate nucleus.

The motor cells of the globus pallidus proper (the paleostriatum) were not reduced in number, and in comparison with the giant pallidal cells of the neostriatum were well preserved. Many of these cells gave the impression, however, of being somewhat reduced in size and

of presenting a more rounded and angular appearance than do normal cells. Their internal structure, including the nucleus and nucleolus was well preserved.

In serial sections, stained by the Weigert-Pall method, certain pathologic changes were also apparent in the corpus striatum (Figs. 3, 4, 5, 6, 7 and 8). The medullary network of the globus pallidus, especially in its anterior portion, had suffered some reduction in the number of its nerve fibers and the external segment had apparently suffered more in this respect than had its internal segment. The reduction was present in both the external medullary and the supplementary external

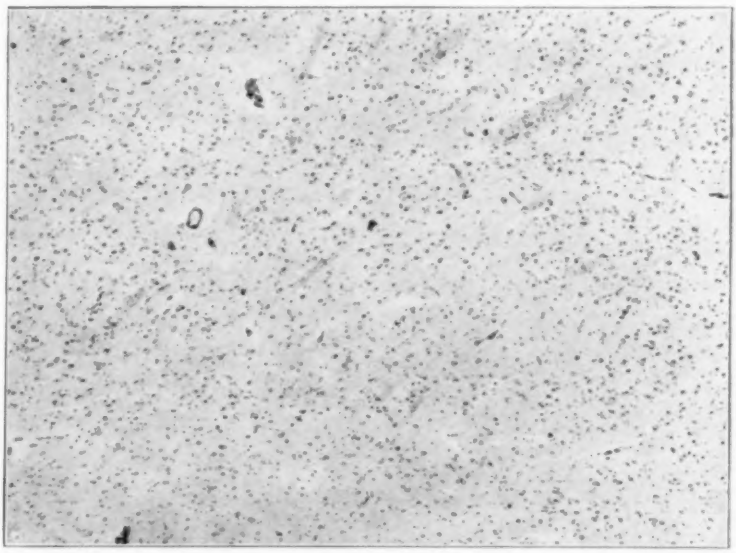

Fig. 10.—Juvenile paralysis agitans of twenty-five years' duration. Section through the putamen. Toluidin blue, × 384. Note the increase of glia nuclei and almost complete absence of the large pallidal cells. The small ganglion cells are not reduced in number.

medullary layer. The ansa system, namely, the strio-hypothalamic radiations, also showed some thinning and atrophy of its fiber systems.

These alterations in the medullary network and radiations of the corpus striatum were diffuse and not sharply defined. They were nevertheless unmistakably present.

The evidences of chronic cellular atrophy in the neostriatum were quite definite and distinct and because of their chronic character could not have been the result of pyrexia or of the terminal infection to which both patients succumbed.

The motor cells of the corticospinal system were quite intact. The large cells of Betz in the rolandic area were well preserved, as were also the large multipolar cells of the anterior horns of the spinal cord. Furthermore, there were no evidences of atrophy or sclerosis of the pyramidal tracts either in the brain or in the spinal cord.

With the exception of pathologic changes in the efferent pallidal system noted above, namely, chronic atrophy of the giant pallidal cells of the neostriatum; a reduction in the fiber network of the globus pallidus and atrophic thinning of the fibers of the ansa system, the central nervous system appeared normal.

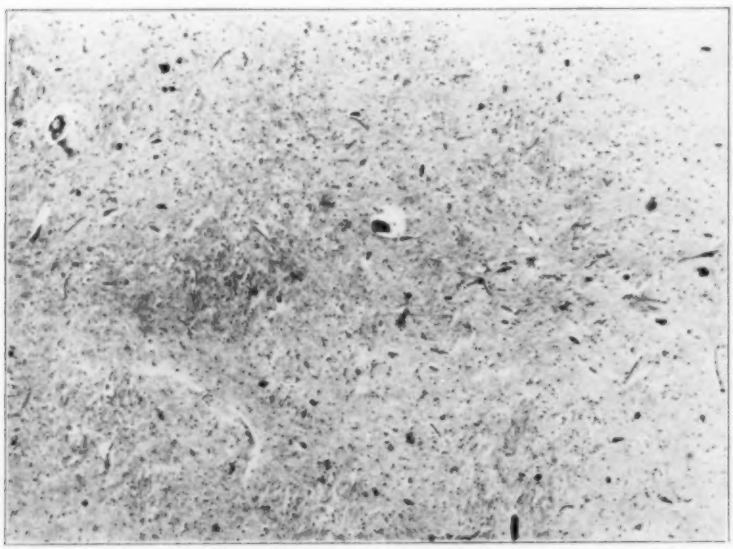

Fig. 11.—Juvenile paralysis agitans of twenty-five years' duration. Section through the globus pallidus. Toluidin blue, × 384. Showing atrophy and diminution in number of the motor cells of the globus pallidus. Note the increase of glia nuclei and numerous irregularly formed concrements.

Histologic studies of sections from the cerebral cortex, the cerebellum, optic thalamus, pons, medulla and spinal cord revealed no lesions which could be offered as an explanation for the phenomena of the disease.

COMPARISON OF LESIONS WITH THOSE OF JUVENILE PARALYSIS AGITANS

It is not without interest to compare these pathologic changes with the histologic findings in juvenile paralysis agitans of twenty-five years' duration reported in my earlier monograph. In this case a study

of the central nervous system by modern histologic methods showed no lesions, excepting of the corpus striatum. In this region the cells of the globus pallidus type were diminished in number; the reduction estimated by comparative cell counts varied from one-sixth to one-half the normal. The greater number of the remaining cells were in various stages of chronic atrophy. These cellular changes were not confined to the cells of the globus pallidus proper, but were also evident in the globus pallidus cells of the caudate nucleus and putamen. The cellular atrophy was therefore confined to a single type of cell, namely, that of the pallidal type. This was apparent in the globus pallidus proper, also in the caudate nucleus and putamen — the neostriatum (Figs. 10 and 11).

Fig. 12.—Juvenile paralysis agitans (Weigert-Pal method). Horizontal section through the cerebral peduncle and basal portion of the corpus striatum. Note the thinning of the ansa peduncularis.

There was also a moderate increase of the glia cells of the globus pallidus, and of the putamen and the caudate nucleus. There was, however, no increase of the glia fibers. This was regarded as a replacement manifestation, secondary to the atrophy of the motor neurons of the pallidal system. The blood vessels of the corpus striatum showed in certain areas a moderate thickening; there were no occlusions and no evidences of any serious vascular or perivascular disturbance.

Corresponding to the atrophy of the efferent cells of the pallidal system, there was a moderate thinning of the striohypothalamic radiations, namely, the lenticular bundle of Forel, the strio-luysian fibers

and the ansa lenticularis and peduncularis (Fig. 12). This diminution was moderate in degree and was evenly distributed. The medullary network of the globus pallidus also appeared to have undergone some slight diminution, but this was difficult to determine by the Weigert method, and, if present, it was evenly distributed and moderate in degree.

The only discoverable lesion was a widespread atrophy and disappearance of the cells of the pallidal system, which I would regard as the essential motor or projection system of the corpus striatum.

A certain harmony in the pathologic changes in the three cases of paralysis agitans therefore exists.

In all, the cellular atrophy was limited to the large motor cells of the corpus striatum (pallidal system) with preservation of the small ganglion cells of the neostriatum (neostriatal system). In all, there were also evidences of atrophy in the ansa system — the striohypothalamic radiations with some reduction in the medullary network of the globus pallidus.

The greater degree of involvement in the juvenile case I would explain by the longer duration of the malady, twenty-five years, in comparison to the two cases recorded in this paper in which the duration of the disease had not exceeded ten years. The longer duration of the disease would account for the greater atrophy and diminution in number of the pallidal cells, the marked increase of glia nuclei and the cellular atrophy in the globus pallidus proper (paleostriatum). The evidences of atrophy in the motor cells of the globus pallidus proper in the two cases described in this paper were only slightly indicated by a somewhat doubtful reduction in size of the cell body and a slight rounding and angularity of outline as compared with normal cells, minor changes which would only have a significance taken in conjunction with the more marked changes in the neostriatum and the very evident alterations in these cells in the juvenile paralysis agitans case.

There is, I believe, a certain analogy between the histologic findings in the corpus striatum in cases of paralysis agitans and those demonstrable in the precentral convolution of the rolandic area in cases of primary lateral sclerosis. In this latter affection it was long held that the large motor cells of the cerebral cortex were not affected and that the lesion was confined to the more distal portion of the primary motor neuron which gradually progressed centripetally.

Later investigations, however, have shown a considerable deviation from the normal which varies directly with the duration or severity of the disease. These cellular changes may range from simple atrophy of the cell to complete destruction, there remaining only cellular rests and fragments.

It is, I believe, not without significance that these two system diseases of central motor tracts should present variations in the degree of the cellular changes in harmony with the duration of the clinical picture, and that the character of the cellular changes should be essentially the same (abiotrophy).

THE SYMPTOMATOLOGY OF PARALYSIS AGITANS

The observations on symptomatology which are summarized in the following pages were carried out in the neurologic wards of the Montefiore Home and Hospital, the wards and outpatient department of the New York Neurological Institute and in my private practice during the past two years. Over fifty cases were utilized, representing various stages and types of the disease.

The symptomatology of paralysis agitans has been so thoroughly investigated by the most distinguished clinicians of the past and present that but little may be added in the way of new observations. The character of the paralysis, the tremor and the rigidity have all been carefully studied by Zingerle,[8] Förster[9] and many others, and the peculiar loss of the automatic and association functions of motility was especially emphasized by Zingerle.

My studies in the symptomatology are therefore in the main confirmatory of the results achieved by other observers, but approached from a new point of view, namely, that paralysis agitans is not a disease, but a characteristic type of central palsy resulting from a lesion in the pallidal system of the striospinal mechanism.

The cardinal symptoms of paralysis agitans are three in number, and consist of *paralysis, rigidity* and *tremor*. The great variation in the clinical picture is dependent on the extent of involvement of the musculature and the degree in which these three fundamental symptoms are present.

In the common form of the disease all three symptoms are usually present in combination, there being simply a tendency to gradual progression.

In other cases, especially in the earlier stage, one symptom may dominate the clinical picture or even be present alone, so that certain special types are recognized. For example, there is a rigid type, the paralysis agitans *sine agitatione,* and a rare *tremor type,* the paralysis agitans *sine rigiditate*. Of these two types, the rigid form is by far the more common and constitutes, in some of the larger

8. Zingerle: Ueber Paralysis Agitans, Jour. f. Psychol. u. Neurol., 1909, **14,** 81.

9. Förster: Ueber Coordinationsstorungen bei Paralysis Agitans, Berl. klin. Wchnschr., 1912, **49,** 478.

statistics, about 20 per cent. of all cases, the disease running its course with little or no tremor manifestations.

I would also emphasize the rare occurrence of what appears to be a pure *paralytic type* of paralysis agitans in which the typical paralytic disturbances are manifested without evidences of tremor or any noticeable rigidity. Of this type, I have only observed one case and a somewhat similar example has been recorded by Kramer.[10] This type, while rare, is of great interest, and may give rise to considerable diagnostic uncertainty.*

In this connection it is interesting to recall that Förster[11] has described paralysis agitans with hypotonia. In this case the characteristic paralytic disturbances with tremor were present, but without rigidity. Instead, there was a well marked hypotonicity of the musculature.

In this somewhat anomalous group of cases it is possible that we are not dealing with a true system disease, but a special vascular type with involvement of other systems, producing a condition similar to that which has been observed in certain *flaccid types* of hemiplegia.

THE PARALYTIC DISTURBANCES OF PARALYSIS AGITANS

The motor disability of paralysis agitans is dependent on the rigidity and a curious type of palsy, which differs from other forms of paralysis by reason of the nature of the paralytic phenomena. The paralysis is limited to the automatic and associated movements of the body and presents a striking contrast to the corticospinal type of palsy in which there is a loss of isolated synergic, or dissociated movements. It is for this reason that such motor activities as those concerned with

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* Report of Case.—*Paralytic Type of Paralysis Agitans.*—A man, aged 62. Duration of the disease two years. Onset with slowness and weakness of movement, affecting first the arms and later the legs. Gradual progression with subsequent involvement of speech and gait. There is a slight masklike expression of face; the eyes are fixed and staring; speech is slow and monotonous. The gait is slow and shuffling, the arms do not swing rhythmically, but are held inertly by the side. There is no festination. There is no tremor and no rigidity of the musculature. The tendon reflexes are all present and active. The skin reflexes are present. (No Babinski sign.) Sensation is normal. The attitude, gait and facial expression are suggestive of paralysis agitans. There is infrequent winking, poverty of movement, and great difficulty in rising from a sitting posture. There is an absence of the associated movements of extension of the wrist on making a fist (absence of the normal *extensor kick of wrist*), which is so characteristic of this form of palsy. The patient was examined three months later and the above findings confirmed. There was a paralysis of automatic and associated movements of the paralysis agitans type without tremor or rigidity.

10. Kramer: Paralysis Agitans ähnliche Erkrankung, Berl. klin. Wchnschr., 1914, **51,** 1287; Neurol. Centralbl., 1914, **33,** 729.

11. Förster: Paralysis Agitans mit Hypotonie, Berl. klin. Wchnschr., 1913, **50,** 649.

walking, running, sitting, rising, lying and turning in the recumbent posture show such marked and early involvement.

It is, I believe, largely for the same reason that there is so much delay and difficulty in initiating movements, as, for example, in rising from the sitting posture. In such movements the associated activities of massive muscle groups are impaired and it is only by great effort of will that the defective automatic function is replaced by corticospinal activity. The peculiar muscular rigidity is also a powerful factor in causing slowness and delay in the initiation of movement and will be discussed more in detail under the heading of rigidity.

If a fairly well advanced case of paralysis agitans is observed at rest, one is impressed by the unusual motor passivity of the individual. The expression of the face, as reflected by the muscles, does not change with variations of the mood. Such emotions as sorrow, joy, surprise and anger find their chief or perhaps only expression in the eyes. An apparent exception would seem to be the smile, as many cases of paralysis agitans are capable of a fairly bright smile. It is, however, a cortical smile and one that a normal person often simulates in a conventional way without any corresponding sensation of joy. These patients, however, are rarely capable of laughter, that is, good hearty laughter in the complete sense, with its complicated series of automatic and associated activities. One is also struck by the absence of the usual gestures and similar associated motor activities which automatically accompany conversation and social intercourse. Even an automatic act such as winking, which is to a large extent of reflex origin, is diminished in frequency, and infrequency of winking has long been recognized as a curious symptom of the disease.

The sufferer from paralysis agitans may be in a sorrowful mood, and the eyes not infrequently fill with tears, but sobbing or crying with all its manifold associated acts is but rarely observed, and practically never in the later stages of the disease. The same may be said of anger, the motor expression for which is generally impaired in tone of voice, facial expression and gesture.

This is also true of such complicated automatic acts as coughing and yawning, which are not manifested in their complete motor form in this disease and yet are unimpaired in the palsies of spastic or corticospinal origin.

In the act of *voluntary* coughing, which is often feeble, the associated contractions of the latissimus dorsi are occasionally absent.

Especially interesting for motor studies are those cases of hemiplegic type in which the paralysis and rigidity are strictly unilateral. In such a case it is possible to observe the normal play of facial expression on the unaffected side with well marked evidences of the

mask on the paralyzed side. It is usual to find under these circumstances that the nasolabial fold has disappeared and also that the slight creases of the forehead have faded from the paralyzed side showing in a slight degree the loss of this controlling mechanism for facial expression.*

I have also noted in these unilateral types absence of the associated movements of the auricle on elevation and contraction of the brows and the frontalis muscle, a very suggestive loss, as such movement must be phylogenetically very old and therefore under striatal control.

The purely reflex act of swallowing is not generally impaired even in the last stages of the disease and we have observed quite advanced cases with complete anarthria and general rigidity when solid and liquid nourishment could be taken without great difficulty by means of the purely reflex mechanism of deglutition.

The same lack of motor association is often noticeable on looking toward the right or left. The eyes turn, but without the usual associated movement of the muscles of the neck which move the head conjointly with the movements of the eyes; also on looking upward, not infrequently the associated contraction of the frontalis muscle fails, in contrast to the normal associated movements which distinguish this act.

If an irritating or unpleasant odor is held before the nose, there is a withdrawal of the head, but the movement lacks the emotional expression of disgust or irritation both in the face and in general character of the withdrawal manifesttations.

It may be added that while some of the above symptoms or, indeed, many of them, may be observed in advanced cases of the disease, it is not to be assumed that they are all present in any given case as the affection is but slowly progressive and the patient usually succumbs from some intercurrent disease long before his automatic and association motor mechanism is completely destroyed.

PARALYSIS OF ASSOCIATED MOVEMENTS OF THE ARMS

Very interesting defects in the association of movement are manifested in the upper extremities. For example, one of the earliest and most characteristic symptoms of the disease is the loss of rhythmical associated movements of the arms in walking. The patient with paralysis agitans walks with the arms held stiffly by the side.

* NOTE.—I have elsewhere[12] expressed the view that the regulating center for the emotional innervation of the face is situated in the anterior portion of the corpus striatum and not in the optic thalamus as is held by many observers.

12. Hunt, J. Ramsay: The Efferent Pallidal System of the Corpus Striatum. A Consideration of Its Functions and Symptomatology, Tr. Am. Neurol. Assn., 1917, p. 10 (Jour. Nerv. and Ment. Dis., 1917, **44**).

Under normal conditions the arms swing alternately with the legs in walking or running, thus simulating the use of the forelegs in quadrupeds. Dupré[13] quite correctly interprets this phenomenon as a vestigial manifestation—a remnant in the biped of a more primitive quadruped gait.

This rhythmical action of the arms in walking, running and jumping is lost comparatively early in the disease, and yet the ability to voluntarily swing the arms shows no impairment.

Again, if the attempt is made to open the hand the fingers slowly unfold and extend but there is not the marked abduction of the thumb and spreading of the fingers which takes place normally; and if the hand is closed quickly, as in grasping an object firmly, the fingers flex and are folded into the palm, but without the sharp associated movement of extension of the wrist, which is present in every normal person (absence of the extensor kick).

It is of interest to recall that the phenomenon of simultaneous extension of the hand on making a fist is increased in spastic paralysis, the so-called "radialis phenomenon" of Strümpel, the absence of cortical inhibition in such cases permitting its more complete expression. It is an involuntary associated movement which permits of a firmer grasp of an object by elongating the points of insertion of the flexor muscles of the forearm. This movement together with the abduction of the thumb and spreading of the fingers are phylogenetically older movements which were of great importance in the "climbing period" of our ancestry, and which still subserve a useful function. (A similar mechanism may possibly underlie the spreading movements of the claws observed in cats.) This absence of the *extensor kick* of the dorsum of the hand is not only an important and early sign of paralysis agitans, but together with the absence of the alternating rhythmical swing of the arms in walking constitutes an important sign of other clinical types of pallidal palsy from focal lesions of the corpus striatum (Hunt).[14]

The loss of other forms of associated movements of the upper extremities are also occasionally observed; for example, the contralateral contraction of the erector spinae group on swinging the arms forward or on abduction of the arm to a horizontal position.

PARALYSIS OF ASSOCIATED MOVEMENTS OF THE LEGS

In movements of the lower extremities a similar loss of muscle association may be demonstrated. In walking, for example, there

13. Dupré, Ernest: Origine Ancestrale et Signification quadrupéde des Movements des bras dans la Marche humaine, XII Cong. Internat. d. med., Moscow, 1897, **2**, 82, Sect. Anat.

14. Hunt, J. Ramsay: Clinical Types of Paralysis Referable to the Pallidal System of the Corpus Striatum, Tr. Assn. Am. Phys., 1918.

is a failure of the associated flexion of the thigh, knee and foot, which accompanies the normal act. Instead, the foot hangs as the knee is lifted which gives the slow dragging movement and shuffling gait which is so characteristic of the disease. Such phenomena as propulsion, retropulsion and lateropulsion may be explained by the loss of the normal associations of movements between the leg and trunk muscles which are a part of the upright posture and the act of walking.

Another very interesting loss of associated movement may sometimes be observed in the lower extremities. Under normal conditions while lying in the recumbent posture if the attempt be made to elevate one of the legs, the effort is accompanied by a very distinct contralateral pressure of the heel of the opposite side against the floor or the bed. It is a contralateral associated movement which is of material assistance in the elevation of the extremities and has been utilized by Dr. Hoover as a differential sign between the hemiplegia of organic and functional origin. This contralateral movement is absent in hysterical hemiplegia because of the absence of the psychic effort of innervation; it is, however, increased in the ordinary spastic hemiplegia of pyramidal tract origin. In paralysis agitans this phenomenon, however, is not infrequently absent, the contralateral pressure of the heel being absent or diminished because of the loss of normal association of movement. The absence of the contralateral pressure of the heel on elevation of a paralyzed extremity may be demonstrated very readily in some hemiplegic types of this disease.

PARALYSIS OF THE ASSOCIATED MOVEMENTS OF THE TRUNK

Very grave disorders of association are also to be observed in movements performed by the trunk muscles, probably because the most important function of these large muscle groups are concerned with automatic and associated movements. The trunk muscles are phylogenetically the oldest of the skeletal muscles, antedating in their origin those of the extremities. It is, therefore, not surprising to find a grave disorder of their function in paralysis agitans, a paralytic affection produced by the loss of the efferent motor neurons of the corpus striatum.* The disturbance of trunk movements are often disproportionately affected as compared with movements of the legs and upper extremities, especially the latter. The movements of the upper extremities unquestionably having a much closer relation to corticospinal or acquired movements than have those of the trunk.

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*NOTE.—On theoretical grounds it would seem to me probable that the trunk muscles because of their phylogeny are closely related to the globus pallidus or *paleostriatum*, while the muscles of the extremities including the head, are more closely correlated with the *neostriatum*.

It is often extremely difficult for cases of paralysis agitans to turn in bed, to sit up, or perform other simple movements of the trunk. On lying down they fall back, the legs rising helplessly in the air, there being no effort made to regulate this movement by extension of the thighs which would tend to counteract the tendency to roll backward with the legs in the air. Furthermore, on attempting to rise from the recumbent posture, with the arms folded on the chest the effort often fails as there is not the initial flexion of the hips and subsequent fixation of the lower extremities thus permitting the use of the ileopsoas muscles in elevation of the trunk. The patient falls backward, the legs rising helplessly in the air.

Very striking is the absence of association movements of the arm and shoulder muscles when the examiner offers his hand for the assistance of the patient while attempting to rise from the recumbent or sitting posture. The hand of the examiner is taken but is merely touched or is held very lightly in a perfunctory manner, and no energetic effort is made to utilize this additional source of aid. The patient rises but without any force being expended by the arm in an effort to assist by pulling or lifting. The absence of spreading and grasping movements of the hand is here manifested in a larger way by the inability to assist the massive movements of the trunk by pulling and lifting movements of the arms. It would seem as if the examiner's hand were taken simply as a matter of form or habit and the rising is accomplished without the slightest assistance therefrom. This is one of the striking examples of the peculiar type of motor palsy with which these cases suffer, and may be readily demonstrated in advanced and comparatively helpless types of the disease.

A similar defect may be observed on rising from the sitting posture. A quite helpless patient will try laboriously to rise from an armchair, without the use of the arms, or if the hands appear to be used it can readily be shown that this is only apparent and that no real pressure on the arms of the chair is exerted. Furthermore, such helpful associated movements as leaning forward and placing the heels well beneath the chair before making the attempt to rise, are entirely disregarded and the attempt is made under what to a normal person would be the most difficult mechanical conditions.

Also, on sitting down, this comparatively simple act is usually performed quite grotesquely by a patient with paralysis agitans, so that the fall is not broken, and they sit down hard, the legs tending to rise in the air as they fall back in the chair. This defect is due to the same lack of association of movement—the heels not

being first placed well beneath the chair and the arms of the chair firmly grasped, as would be the natural course of events in other types of motor disability.

Perhaps, there is no more beautiful demonstration of the loss of this association mechanism than occurs if the patient while standing on a large mattress is quite suddenly pushed over. In advanced cases of the disease, the fall is passive and complete, and occurs without any of those muscular attempts to break the fall which are present in all other conditions of palsy, even in profoundly spastic states. The patient falls, silently and stiffly, like a marble statue and oscillates to and fro in the same manner as would any solid or immobile object.

PRESERVATION OF ACQUIRED MOVEMENTS IN PARALYSIS AGITANS

In striking contrast to losses in the sphere of the automatic and association activities of movement is the preservation of specially acquired movements of cortical origin. These are carried out quite correctly in every detail, except for the difficulties produced by the tremor, rigidity and the paralysis of associated movements. A case of shaking palsy which has lost the alternating rhythmical swing of the arms in walking, the spread of the fingers and abduction of the thumb, the extensor kick of the wrist and the other paralytic disturbances enumerated above will take off his coat, draw up a chair, pick up a pencil from the floor and proceed to write, all the movements being quite correct in their detail execept for the rigidity and tremor.

The motor disturbances just enumerated, therefore, involve the associated and automatic movements. Motor activities which are phylogenetically old and which are automatic and involuntary in character. It is very likely that this form of motor activity had reached an advanced stage of development in the lower forms of life, and that further additions to the wealth and variety of motor activities coincide with the appearance and evolution of the cerebral cortex.

This older mechanism which governs the association of movement retains, however, its full activity in man and is utilized in many, if not all, cortical movements. It would be difficult to conceive of any but the simplest motor acts of cortical origin in which the older mechanism does not play some rôle. Many acquired movements subsequently become more or less automatic, as for example, brushing the teeth, shaving with a safety razor, hammering, etc. Such acquired activites are not infrequently lost or seriously disturbed early in the

course of paralysis agitans, probably because of the preponderant automatic component of striatal origin.*

RELATIONS OF THE CEREBRAL CORTEX AND THE CORPUS STRIATUM

The nature of the mechanism by which the cortical and striatal activities are harmonized is largely speculative. It now appears highly probable that the corpus striatum has no direct connection with the cerebral cortex. The pyramidal tracts, however, as they traverse the striatum send off numerous collaterals to all parts of this structure, so that a certain relationship between the motor cortex and the corpus striatum could be maintained through the medium of such collateral fibers. The optic thalamus also stands in very close relationship with all portions of the cerebral cortex by its afferent and efferent fiber systems; and as very close intimate associations exist between the thalamus and the corpus striatum the influence of the cortex on the striatum could be exercised in this manner.

In order that a structure should play the rôle which I would ascribe to the corpus striatum, it must have very intimate connection with the proprioceptive system and the cerebellum. Such a relationship surely exists for the corpus striatum through its very close association with the optic thalamus which has such direct and important connection with both the cerebellum and the general sensory system. I assume, therefore, that the motor system of the corpus striatum is essential for the control of automatic and associated movements, and that it exercises this function through the medium of the rubrospinal system and other extrapyramidal motor tracts which as yet are but imperfectly understood, the existence of which, however, cannot be denied.

IMPORTANCE OF THE EXTRA PYRAMIDAL SYSTEM IN MOTILITY

The importance of the extrapyramidal system is shown very beautifully in the development of motility in the fetus. At the eighth month

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* NOTE.—Realizing the peculiar nature of the motor disturbance in this disease, I have made some systematic efforts to restore by *reeducation* the loss of the more important automatic and associated movements. Attempting to substitute a cortical activity for the loss of the striatal mechanism. The difficulties are very great because of the very nature of the lost movements, their involuntary and automatic character.

However, something may be accomplished by substitution for the more important movements. The principle of this form of reeducation is to teach the patient the manner in which such movements, as rising from a sitting posture, sitting down, walking, turning, etc., are performed so that the victims of this disease may gradually acquire consciously what they previously performed unconsciously and automatically.

of fetal life Van Gehuchten[15] has shown that the spinal cord contains no pyramidal tract fibers, the axis cylinders not yet having descended below the level of the pyramidal decussation of the medulla oblongata.

Hence all nerve impulses to the muscles of the extremities before the eighth month of fetal life must pass by way of other motor tracts, namely, the extrapyramidal system.

If we observe an infant born prematurely at the seventh month, one cannot but be impressed by the variety and strength of movements which show the characteristic qualities of striatal motility. The early myelinization of the ansa system of the corpus striatum which appears about the fourth month of fetal life, therefore, acquires a new significance in the light of the more active fetal movements which begin at this period and their probable striatal origin.

In conclusion, it may be stated that this very complicated striospinal mechanism in man finds a very simple counterpart in the lower forms of life and is represented by the globus pallidus (paleostriatum), the basal forebrain bundle of Edinger, and the primary motor fasciculus of the spinal cord. These structures constitute the primitive motor system of fishes which have only a rudimentary cerebral cortex and yet are endowed with a rich capacity for automatic and associated movements.

THE RIGIDITY

A conspicuous symptom of paralysis agitans and one which contributes very materially to the general motor disability is the rigidity. Stiffness of the musculature is a large factor in producing that slowness of movement which with loss of the automatic and association activities of muscles cause the peculiar facial expression, attitude and gait, which are so characteristic of the disease.

This rigidity is unquestionably of central origin, as is the spasticity which characterizes the paralysis of pyramidal tract disease. It, however, presents certain differences, the explanation for which will be offered later.

The muscles are quite firm to touch, their contour is well defined and there is a state of continuous hypertonicity which gives to passive movements an impression of waxlike rigidity. In this respect the hypertonia of paralysis agitans differs from that of spastic paralysis. It is more plastic, while that of the spastic state is more elastic in character. Passive movements in paralysis agitans show that the continuous rigidity is often broken by a peculiar rhythmical sensation due to an intrinsic *tremor tendency* of the muscle substance. This

15. Van Gehuchten: Faisceau Pyramidal et Maladie de Little, Jour. de neurol. et d'hypnol, 1896, **1**, 225.

muscle manifestation, or cogwheel rhythm as it is sometimes called, is more apparent in those forms of the disease in which tremor is well marked and, when present, is a very characteristic sign.

Both forms of hypertonicity, spasticity and rigidity are increased by irritation of the skin, by cold and by mental excitement; both are diminished by rest, warmth and sleep. The spastic state is further characterized by certain clonic phenomena and exaggeration of the tendon reflexes. In paralysis agitans, muscle clonus and reflex hyperexcitability are absent, except for occasional pseudoclonus or tremor clonus in the earlier stages of the disease. In the spastic state, however, a certain elastic quality of hypertonicity is more in evidence. In the rigidity of paralysis agitans the plastic component predominates — and this constitutes the chief difference between these two forms of hypertonus.

It is generally held that the hypertonicity of spastic states is caused by a loss of the cerebral inhibitory function and when the connections between the motor cortex and the motor cells of the spinal cord are severed, spasticity results. It would thus appear that a higher motor center in order to be effective, must control the spinal mechanism which is engaged in the regulation of tonus, and when this control is lost hypertonicity results. A similar explanation may be offered for the occurrence of rigidity in paralysis agitans.

According to my conception, this disease is the result of an atrophy of the essential motor projection system of the corpus striatum — the pallidal system, which exercises a controlling influence on the lower spinal mechanism through the medium of the extrapyramidal motor tracts.

As the corpus striatum represents a higher controlling motor mechanism, although phylogenetically much older than the corticospinal system, it also must control or inhibit spinal tonus, and when this inhibition is lost, hypertonicity of the musculature results.

There are certain peculiarities in the quality of this hypertonicity which I would ascribe to differences in the relationship of the corticospinal and striospinal systems to the peripheral nerve distribution and the constituents of the muscle fiber (Hunt[16]).

THE INTRINSIC CONTRACTILE SYSTEMS OF STRIATED MUSCLES AND THEIR DUAL INNERVATION

The voluntary musculature of the body belongs to the group of striated muscles which is composed of two distinct substances or

16. Hunt, J. Ramsay: Preliminary Report on the Evidence Indicating the Existence of a Paleokinetic and Neokinetic System for the Transmission of Motor Impulses in Peripheral Nerves, Tr. Am. Neurol. Assn., 1918.

systems. The one is the anisotropic disk system which is innervated by the large multipolar cell of the anterior horn, a medullated nerve fiber and the motor end plate of the muscle; the other is the sarcoplasmatic substance which is under the control of the sympathetic system and is innervated by the sympathetic motor cell of the anterior horn, nonmedullated nerve fiber and the terminal sympathetic end-plate of the muscle fiber.

These two muscle systems differ essentially in their histologic, physiologic and chemical characteristics, and each has a separate nerve supply and source of innervation. The anisotropic disk system subserves the function of the twitch or quick contraction and is the predominant factor in the production of voluntary movements. The sarcoplasmatic system, on the other hand, subserves a more plastic function and is especially active in automatic and association movements requiring fixed postures and attitudes. Both components, however, the contractile and plastic, participating in all forms of motility, differing only in degree (Sherington[17] and Langelaan[18]).

The nonstriated, or smooth muscles of the body are innervated exclusively by the sympathetic nervous system and phylogenetically represent a much older system than that of the striated muscles. It is, therefore, not altogether surprising that the striospinal system which controls a lower grade of movement than the corticospinal should show the predominant rôle of the plastic component in contrast to spastic states, with their characteristic clonus and exaggeration of the tendon reflexes, which are manifestations of the contractile components of this form of hypertonicity.

The higher development of motion is therefore attended by a greater activity of the elastic component, which thus permits of a more rapid and more complete control of motor activity. In cortical movements, the anisotropic disk system is therefore the predominant factor.

The evolution of the central nervous system has taken place by a gradual grouping and integration of lower segmental activities under the control of a higher regulating mechanism. For example, in the realm of motility the simple reflex movement of segmental origin has been gradually replaced by the more complicated types of movements represented by automatic and associated acts of striatal origin. Subsequently the isolated or dissociated movements of cortical origin were superadded which find their expression in the various acquired motor activities of man. In this method of development a lower

17. Sherrington, C. S.: Postural Activity of Muscle and Nerve, Brain, 1915, **38,** 191.

18. Langelaan, J. W.: On Muscle Tonus, Brain, 1915, **38,** 235.

mechanism and its more limited forms of movements are not lost, but merely subordinated. All are utilized in that wonderful harmony of perfect movement, yet, underlying this are the various controlling and integrating mechanisms which remain as permanent landmarks of the slow and devious stages of the evolutionary process.

It is, therefore, not unreasonable to infer that the two intrinsic muscle systems of the striated muscle fiber with their dual innervation are under the control of separate correlating centers. The sarcoplasm with its sympathetic innervation differs so fundamentally in its neural, clinical and histologic characteristics from the anisotropic disk system that the probability of a separate controlling mechanism can hardly be questioned.

I would, therefore, postulate the existence of two distinct correlating centers for the control of the striated muscular system; one related to the nonmedullated system and the sarcoplasmic substance of muscle, the other related to the cerebrospinal medullated system and the more highly specialized contractile or anisotropic disk system of muscle.

Both centers are, I believe, under the control of the efferent pallidal system of the corpus striatum. The loss of the inhibitory influence of the motor cells of the corpus striatum in paralysis agitans would release these lower centers from control with the *static* symptoms so characteristic of the disease, namely, tremor and the rigidity. The tremor follows the release of the inhibitory mechanism governing the anisotropic disk system; the rigidity follows the release of the center controlling the sarcoplasmatic substance of muscle. Generally, both tremor and rigidity occur in the symptomatology of the disease. However, in quite a considerable proportion of cases (in some statistics as high as 20 per cent.) rigidity occurs alone, and it is by no means unusual to observe cases of paralysis agitans which throughout their entire course extending over a period of many years have manifested no evidences of tremor. The frequency of such an occurrence appears to furnish strong evidence for the assumption that two separate centers exist — one for the control of contractile, the other for the control of plastic tonus and which may be released independently in the course of the disease.

It has long been held, following the teaching of Hughlings Jackson, that tremor is associated with and is really a part of the rigidity. As he so aptly expressed it, "Tremor is rigidity spread thin, and rigidity is tremor run together." In other words, there is no inherent difference between tremor and rigidity except one of degree.

It is quite true that in the course of paralysis agitans the evidences of tremor disturbance generally tend to diminish with the progress of the disease and the further development of the rigidity. This diminution I would, however, regard as partly mechanical in its origin, the waxlike rigidity and contractures of the musculature diminishing and blocking the tremor tendency precisely as it blocks the freedom of voluntary and associated movements.

Be this as it may, there stands opposed to the Hughlings Jackson theory the frequent occurrence of the rigid type of paralysis agitans, progressing without initial tremor in which the character of the rigidity does not differ in any respect from that which accompanies cases with well marked tremor. This theory then would not adequately explain all of the types and various manifestations of the disease. It would therefore seem reasonable to postulate the existence of two distinct centers for the control of the muscle tonus of striated muscles: one a *center for contractile tonus* which regulates the anisotropic disk system through the medullated nervous system; the other a *center for plastic tonus* which regulates the sarcoplasmatic substance through the nonmedullated nervous system. Both of these tonus centers are under the control of the pallidal system of the corpus striatum, the loss of which may be registered by tremor or rigidity according to the system involved.

THE TREMOR

The third characteristic symptom of paralysis agitans is the tremor. This curious motor disturbance consists of an involuntary tremor movement, rhythmical in character, varying from three to five vibrations to the second. It continues during rest and is therefore spontaneous and not dependent on movement or posture. It is, however, in no sense an intention tremor as this term is used to describe a tremor. It often, however, shows the characteristics of an action tremor, increasing during the passage of the movement but diminishing or ceasing as the end of the passage of the movement is reached—as, for example, when the finger is carried to the tip of the nose. Like another involuntary motor manifestation — chorea — it may be exaggerated by incidental occurrences. For example, both are increased by mental excitement and by motor activity. Both usually diminish during mental and physical rest; both cease during sleep. There are apparent exceptions to this latter statement in severe cases or perhaps when sleep is not profound.

The tremor of paralysis agitans has the same *tempo* in all of the parts affected, and at times nearly all muscles may be involved, including even those of the vocal cords and eyeballs.

THEORETICAL CONSIDERATIONS ON THE ORIGIN OF TREMOR

Speculating on these various involuntary motor phenomena such as tremor and chorea, it has seemed to me not unlikely that the development of motility has followed a certain scheme in the evolutionary cycle, which may be summarized somewhat as follows: The earliest types of motility were represented by slow plastic movements of the sarcoplasm of reflex origin under the control of the sympathetic nervous system. Subsequently, with the development of striated muscles and the anisotropic disk system, the quick contractions of reflex origin followed under the control of the medullated or cerebrospinal nervous system.

The next step in the development of motility was the ability to perform quick to and fro movements with its correlating and inhibitory mechanism. Later, the ability to perform associated movements was developed and last of all, the isolated and dissociated movements of cortical origin, each group of motor activities having its own controlling and inhibitory mechanism.

As these various integrations of neural development were superadded one on the other in the long process of evolutionary development, they were harmoniously welded together. Each mechanism having reached a certain stage of development probably remained stationary, the evolution of motility proceeding along other lines. In this manner, we would have a nervous system whose constituents, while welded together and acting harmoniously, represent successive and distinct stages of motor development.

A loss of any connecting link in this chain of motor groupings would be followed by certain characteristic symptoms. Each link as it is superadded would control or inhibit the previous group, as such control would be necessary if higher motor activities are to be performed.

A loss of the small association and inhibitory cells of the neostriatum (neostriatal system) as occurs in Huntington's chorea is followed by the choreiform movements which are characteristic of this disease. The loss of this inhibitory mechanism releases the pallidal system of the corpus striatum from control, and as a result we have the involuntary associated movements which characterize certain diseases of striospinal origin (Hunt[7]).

A loss of the *efferent pallidal system* as occurs in paralysis agitans, releases other lower controlling and inhibitory centers from control. One of these is the center for the control of contractile tonus and the anisotropic disk system of striated muscle. When this is released, a tremor results which is characteristic of shaking palsy, the

disk system falling into involuntary, rhythmical to and fro movements which is one of the more primitive forms of motility.

The other is a center for the control of plastic tonus and the sympathetic system of muscles, and when this is released rigidity results.

The tremor of paralysis agitans I would, therefore, regard as an involuntary form of motor activity, not dependent on the rigidity per se as was suggested by Hughlings Jackson, but produced by loss of the inhibitory function of the pallidal system on a lower mechanism governing rhythmical movements of the anisotropic disk system of striated muscles.*

GENERAL SYMPTOMATOLOGY

The essential and characteristic symptoms of paralysis agitans are those which have just been considered, namely, a paralysis of automatic and associated movements, the waxlike rigidity and spontaneous rhythmical tremor. All of these symptoms I would refer to atrophic changes in the *pallidal system* of the corpus striatum.

Paralysis agitans is, therefore, a special type of central palsy, due to a loss of function of the striospinal system, in contradistinction to spastic paralysis, which results from disease of the corticospinal system. It is properly speaking, therefore, not a disease but a characteristic type of palsy which may result from a variety of pathologic lesions.

Among these may be mentioned such conditions as senile atrophy, vascular degeneration, and various gross lesions of the corpus striatum, for example, softening, hemorrhage, tumors, encephalitis and syphilis. In a recent study,[14] I have directed attention to various clinical types of palsy referable to vascular lesions of the corpus striatum characterized by hemiplegia, monoplegia and diplegia of pallidal origin.

Paralysis agitans may, therefore, be regarded as a characteristic type of central palsy which may be produced by a variety of lesions, and is properly speaking a syndrome and not a definite disease. Ménière's disease, which was so long regarded as a distinct affection, has been gradually resolved into a number of pathologic entities; this, I believe, will be the fate of Parkinson's disease. According to my

* NOTE.—The possible relation of a primitive tremor mechanism to early heat production in warm-blooded animals is not without interest. Barr and DuBois[19] have recently shown in calorimeter studies that the reduction of body temperature below a certain point is immediately followed by algid tremors with corresponding increase of heat production and rise of temperature. In this connection it is also of interest to note that according to Zingerle there is a slight elevation of temperature in about 23.4 per cent. of cases of paralysis agitans which may have some bearing on the subjective sensations of heat and flushing which are not uncommon in this disease.

19. Barr and DuBois: Metabolism in Malarial Fever, THE ARCHIVES INT. MED., 1918, **21**, 654.

conception it is a syndrome, characterized by a special group of symptoms — paralysis, rigidity and tremor — but referable to different types of pathologic lesions and various disease processes.

Many other symptoms associated with our textbook descriptions of paralysis agitans also deserve consideration. These, however, I regard as incidental or complicating factors and not essential to this form of palsy.

As the vast majority of paralysis agitans cases occur in the presenile period of life, many of which last into senility, it is not surprising that evidences of mental disturbance and deterioration are often associated with this disease.

The same is true of certain sensory symptoms, subjective and rarely objective, which are probably referable to associated senile or vascular changes in the optic thalamus. To regard these symptoms as essential to paralysis agitans would be similar to incorporating various sensory symptoms complicating spastic forms of palsy as something essential and characteristic. Such symptoms are referable to the general pathologic processes and are not in any sense peculiar or essential to paralysis agitans.

The various secretory, vasomotor and trophic symptoms are neither constant nor characteristic, and are to be regarded as secondary and not primary manifestations of this form of palsy.

I have already indicated the possible relation of increased temperature to the tremor movements, and some of the vasomotor and secretory reactions may have a similar origin.

In paralysis agitans, however, we are dealing usually with subjects in advanced life and with other evidences of marked senile changes, so that the organic changes in the brain and spinal cord are by no means always limited to the pallidal system

CONCLUDING REMARKS

My conception of the nature and symptomatology of paralysis agitans may be summarized briefly as follows:

The clinical picture to which the term paralysis agitans has been applied, represents a fundamental type of palsy referable to a lesion of the motor system of the corpus striatum. This system takes its origin in the large motor cells of the corpus striatum, namely, in those of the *globus pallidus type*, and terminate in relation to important ganglionic structures of the hypothalamic region, that is, the nucleus ruber, the corpus subthalamicum and the substantia nigra.

This system may be distinguished as the *efferent pallidal system* because of its origin in motor cells of the globus pallidus type.

These cells constitute the chief cellular content of the globus pallidus or paleostriatum (*paleopallidal cells*). They are also present in considerable number in the caudate nucleus and putamen or neostriatum (*neopallidal cells*). The neopallidal cells are of especially large size and constitute veritable giant cells, in this respect suggesting a certain analogy to the giant motor cells of the rolandic area (area giganto cellularis—cells of Betz).

The efferent pallidal system of the corpus striatum is a mechanism for the control of automatic and associated movement, and exerts its function through the medium of the so-called extrapyramidal tracts, namely, the rubrospinal and other extrapyramidal motor systems.

The pallidal system of the corpus striatum may be involved in various types of pathologic processes. There is a *primary atrophy of the pallidal system;* senile atrophy and vascular lesions; gross lesions from hemorrhage, softening tumor — indeed, any pathologic process localized in the course of the pallidal system may produce some of the characteristic symptoms of paralysis agitans. In this respect, the conditions are similar to those of the corticospinal or pyramidal tract system in which various pathologic lesions may produce symptoms of spastic paralysis.

Paralysis agitans is, therefore, referable to a disorder of the striospinal system as spastic paralysis is referable to a disorder of the corticospinal system.

These conclusions are based on the pathologic findings in three cases of paralysis agitans, one of the juvenile type and two of the presenile type, in which definite evidences of selective atrophy were demonstrable in the motor cells of the pallidal system. Corresponding to the atrophy of motor cells there was some thinning and atrophy of the strio-hypothalamic radiations or ansa system.

As the strio-hypothalamic radiations contain abundant afferent as well as efferent fibers, the ansa system appears simply somewhat attenuated and does not present the definite histologic picture of atrophy as is observed, for example, in the pyramidal tracts where the fibers are all efferent and grouped in a compact bundle. Much more distinctive are the evidences of atrophy in the pallidal cells, which stand out quite clearly amidst the normal neostriatal cells of this region.

The characteristic symptoms of primary atrophy of the pallidal system are paralysis, rigidity and tremor. All other symptoms which are described in paralysis agitans I would regard as secondary, or as complications and associated with some special form of pathologic lesion.

The paralysis is characterized by a loss of automatic and associated movements, which are phylogenetically old and represent a lower form of movements than are those of cortical origin. For this reason, such activities as walking, running, rising from a sitting or recumbent posture, grasping, etc., show especial involvement.

The loss of certain automatic and association activities of the muscles of expression are clearly demonstrable in the face. The corpus striatum, therefore, contains the motor center for the emotional innervation of the face.

The rigidity and tremor of paralysis agitans are referred to a loss of striatal inhibition, the corpus striatum controlling muscle tonus as does the cerebral cortex. When this inhibitory function is abolished hypertonicity results.

As the striated muscle fiber has a dual innervation and function, a correlating center or group of centers for the control of these two systems is believed to exist. One of these controls the anisotropic disk system which subserves the function of the quick contraction or the twitch; the other controls the sarcoplasmatic substance and the more plastic contraction of the muscle. It is thought that the independent occurrence of a *tremor* and a *rigid* type of the disease may be explained on the basis of this hypothesis.

We must recognize, therefore, in the central nervous system, three systems which subserve the functions of motility. A *segmental* system with its various reflex functions, the *striospinal* system with its control of automatic and associated movements, and the *corticospinal* system with its higher quality of discriminative and dissociated movements. All three systems represent different stages of evolutionary development, and all are concerned in the elaborate function of motility. Each system as it is superadded utilizes those of earlier development. Therefore, in nearly all movements these various components are represented, the degree of representation varying with the character of the movement.[20]

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20. For complete bibliography consult chapter on Paralysis Agitans in Lewandowsky's Handbuch der Neurologie, Vol. III, pp. 931 and 956.

BOOK REVIEW

MEDICAL WAR MANUAL No. 6. Authorized by the Secretary of War and under the Supervision of the Surgeon-General and the Council of National Defense. Laboratory Methods of the United States Army, Compiled by the Division of Infectious Diseases and Laboratories. Office of the Surgeon-General, War Department, Washington, D. C. Illustrated. Philadelphia and New York: Lea and Febiger, 1918. Price, $1.50.

The money value of medical service including sanitary work is hard to compute, but many clear headed people who know something about the situation believe that much of the cost of our share in the war will be made up within a short time by the increased efficiency of the medical profession. No country in any period has so well prepared the medical service of its armies, none ever put into execution such far reaching training of its medical officers. Most of these will ultimately return to civilian practice.

This little book expresses the spirit of the Army Medical Corps and furnishes the model for such aids to practical work as every house officer and every laboratory worker needs daily. It can easily be carried in the pocket. From the remarks on the "Responsibilities of the Laboratory" and the "General Rules for the Conduct of the Laboratory" to the last paragraph, the book is packed with sound and accurate matter. The reviewer is tempted to quote, but selection is difficult when there is so much excellence. How important is Rule 6: "Label every thing and do it legibly," and Rule 12: "Remember that it is as important to keep accurate records as to carry on accurate tests." In every section are numerous details such as experienced laboratory workers unconsciously use, but that are often unknown to many others. In the under-staffed laboratories of medical schools and civil hospitals such things are likely to be missed in personal teaching, but can be learned by careful use of this manual. The value of the work in places where books are necessarily few can be seen by noting that it contains not only all the most useful methods given in laboratory manuals, but also sections on the sanitary examinations of milk and water; examinations for poisons; purification of water supply, and methods of sewage disposal. Criticism is invited, but little has been found to criticize except minor details. The headings for methods might be better if made uniform. The mixture of bold face and roman, of center and side heads is sometimes confusing. Under blood staining on page 46, it is said that with Wright's stain "sometimes if the preparation looks very bluish and under the microscope the red cells have a greenish blue tinge, the proper pink color can be brought out by washing the smear quickly with a few drops of the original undiluted staining fluid." As given earlier, washing longer with distilled water will do the same thing better. In examining for amebas in feces it is said that "the specimen is fished with a large platinum loop." Considering the need of the government for platinum for other purposes it might be said that two wooden tooth picks serve just as well.

A wide use is predicted for the little volume and much satisfaction from its use.

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